Journal of
CHRONIC DISEASES

VOL. 1 MARCH, 1955 NO. 3

OL.
1
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Original Communications

OPPORTUNITIES AND PROBLEMS IN THE STUDY OF CHRONIC DISEASE IN INDUSTRY

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(Received for publication Sept. 13, 1954.)

THE extent to which industry can contribute to knowledge of the chronic disease problem is a matter of considerable interest to health workers generally and to the population at large, as well as to management and labor. For the latter group, knowledge of the dimensions of the chronic disease problem and of the factors contributing to the occurrence of chronic diseases is of considerable practical importance. Such information is of value to labor and management alike in relation to the increasing trend toward fringe benefits in contracts with unions; it is essential as base-line data in attempting to determine whether or not any particular disease is occupational in origin; it is important in assessing the effect of particular chronic diseases upon the turnover rate of skilled labor. Inquiry into the feasibility of producing the desired information from data arising out of the operations of industrial medical programs is, therefore, amply justified.

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Data concerning one or another aspect of chronic disease are available in the records of pre-employment examinations, visits to the dispensary, sick absenteeism, and periodic physical examinations. From the standpoint of defining the extent of the chronic disease problem and of determining the factors influencing its magnitude, the findings of the pre-employment and the periodic physical examinations should, in theory at least, be the most productive of information. Indeed, the data arising from these examinations are unique in the opportunity they hold out to study the chronic disease problem. With the possible exception of the military, there is no other single activity in our society in which individuals receive periodic medical examinations and in which the findings of these examinations may be related to the demographic, physiologic, and other characteristics of a known population base.

Whether the potential value of the pre-employment and periodic physical examination in adding to knowledge of chronic disease can be realized is dependent upon whether the observations made on the individual employee are, or can be, recorded and organized in relation to the general objectives stated previously, namely, to delineate the dimensions of the problem among employees *as a group* and to identify the factors influencing the size of the problem.

It is the purpose of this paper to examine the feasibility of achieving these objectives with the data available from the employment and periodic physical examinations as conducted in an actual operating situation. The opportunity to conduct such a study arose when E. I. duPont de Nemours & Company, aware of the intrinsic worth of the information in the files of its Medical Division, requested the Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, to examine certain materials available in the Medical Division to determine what light they could throw on the health problems of the Company's employees and whether it was worth while to continue to collect these materials in the same manner.

MATERIALS

The basic materials for this study consist of punch cards made at the Wilmington office from the records of annual physical and employment examinations made in various plants of the Company. Such punch cards are available for as long as fourteen years for many of the plants. At the time the practice of making the punch cards was begun, the findings of the physical examinations, in so far as they were designated as diagnoses or conditions on the record, were coded according to a modification of the 1929 edition of the International Statistical Classification of Causes of Death. This practice has continued down to the present so that there is a consistent procedure which, even though it may yield different values for the frequency of diseases in particular categories than other classifications which have since been devised, nevertheless should permit judging whether the chronic disease problem in industry can feasibly be defined by means of information collected in existing programs.

The analyses of the present study are confined to the data on male employees.

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FINDINGS

1. The first step in exploring the feasibility of describing quantitatively the dimensions of the chronic disease problem among employees of the duPont Company was to determine the prevalence of certain diseases or conditions as found in the different plants of the Company among employees examined in 1952-1953. The particular conditions chosen for examination were high blood pressure,* skin diseases,† respiratory diseases,‡ stomach and duodenal ulcers,§ heart disease,‖ arthritis,¶ diabetes,# cancer,** and diseases of the blood and blood-making organs.††

The prevalence of these various conditions, adjusted to the age distribution of the Company as a whole, is shown in Figs. 1 to 9.

The most striking feature brought out by the graphs is the tremendous amount of variation in the rates for the different plants. Thus, in Fig. 1, the prevalence of high blood pressure appears to vary from a rate of 102.61 per 1,000 males examined in Plant A to less than 9 at Plants Y and Z. The range of variation in prevalence of skin diseases is even greater and for many conditions, such as stomach and duodenal ulcer, a number of plants have a rate which is practically zero, whereas others have rates as high as 50 per 1,000 males examined.

The variation in prevalence among the plants is not confined to the specific diagnoses just considered. There is also great variation in the frequency with which *any* diagnoses are made (Fig. 10). Nearly 9 out of 10 males examined at the G, W, and K plants are recorded as having no clinical diagnoses. By contrast, less than one-half the employees at the C, X, and D plants had no diagnosis recorded.

2. Before considering the possible meaning of the observed variation in prevalence of these conditions among the various plants we shall examine whether there is any indication of change with time in the dimensions of the problem. The age-specific prevalence rates in 1940-1941 and in 1952-1953 for a number of diseases and conditions are shown in Figs. 11-18 for the group of plants on which punch cards were available for this period. Over the fourteen-year span, there has been an apparent increase in the prevalence of skin diseases, duodenal

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*High blood pressure is defined as any reading of 150 mm. Hg or more systolic *and* 95 or more diastolic.

†Skin diseases are recorded in a separate column on the punch card designated "appearance." When a skin disease is present it is punched as such.

‡Respiratory diseases include diseases of nasal fossae and adnexae, diseases of the larynx, bronchitis, lobar pneumonia, pneumonia unspecified, pleurisy, congestion, edema, embolism, and thrombosis of lungs, asthma, pulmonary emphysema, other diseases of respiratory system except tuberculosis, infected, diseased, or enlarged tonsils and adenoids or their removal, Vincent's angina, and sore throat.

§Stomach and duodenal ulcers were recorded as such.

‖Heart disease includes pericarditis, endocarditis, valvular disorders, hypertensive cardiovascular disease, diseases of the myocardium, angina pectoris, diseases of the coronary arteries, auricular fibrillation, cardiac hypertrophy, and heart disease unqualified.

¶Arthritis consists of all forms of arthritis mentioned as such plus a small number of cases of rheumatism, gout, acute rheumatic fever, and sciatica.

#Diabetes includes mentions of diabetes, unqualified, and diabetes mellitus.

**Cancer refers to all cases of a particular site classified as malignant.

††Disease of blood and blood-making organs includes hemorrhagic conditions, anemias, leukemias and pseudoleukemias, diseases of the spleen, others.

ulcers, heart disease, arthritis, and diabetes. In some instances, such as diabetes and stomach and duodenal ulcers, the increase is quite marked. In the case of high blood pressure, on the other hand, no increase is noted in the graph (Fig. 11).

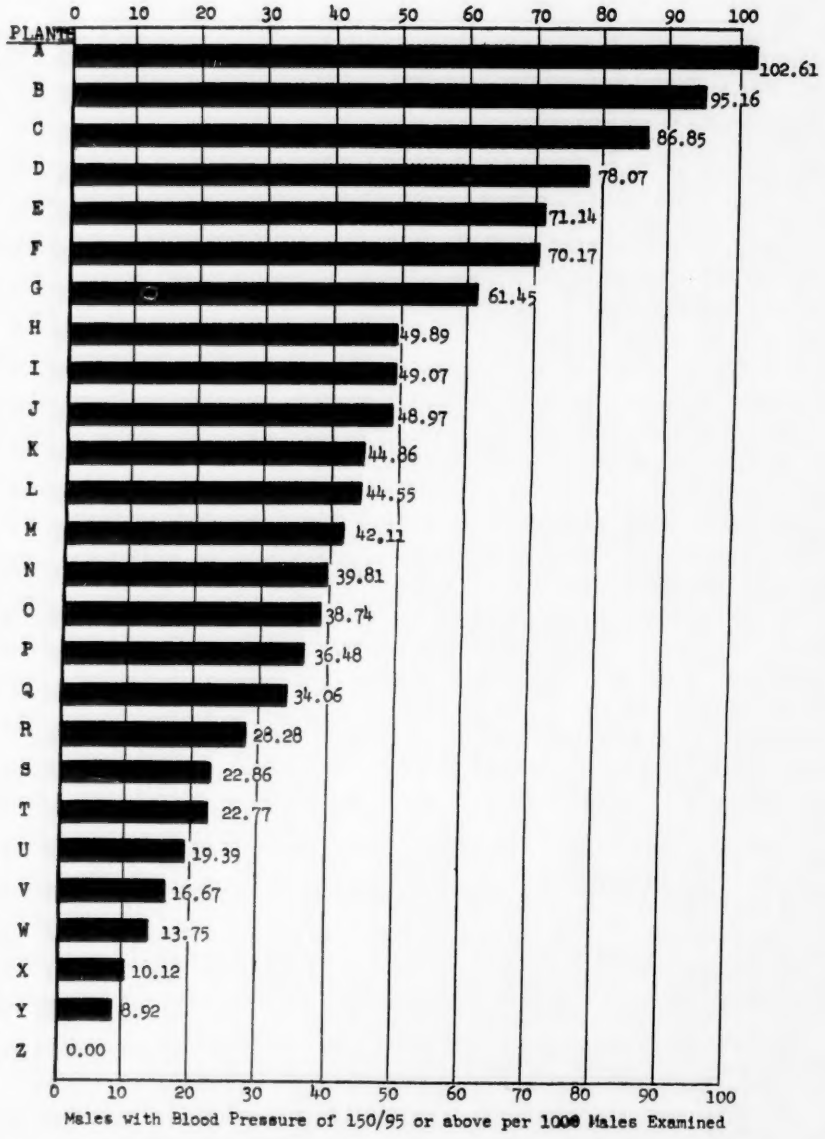

Fig. 1.—Prevalence (rates standardized for age to company age distribution) of high blood pressure per 1,000 males examined by plants, 1952-1953.

Thus, there appear to be great variations in prevalence of chronic diseases among the plants at a particular time and there are also variations in the apparent prevalence of certain conditions in the group of plants over a period of time.

The prevalence of disease may be examined from still another point of view. Prevalence at any time is the cumulative result of the prior operation of various

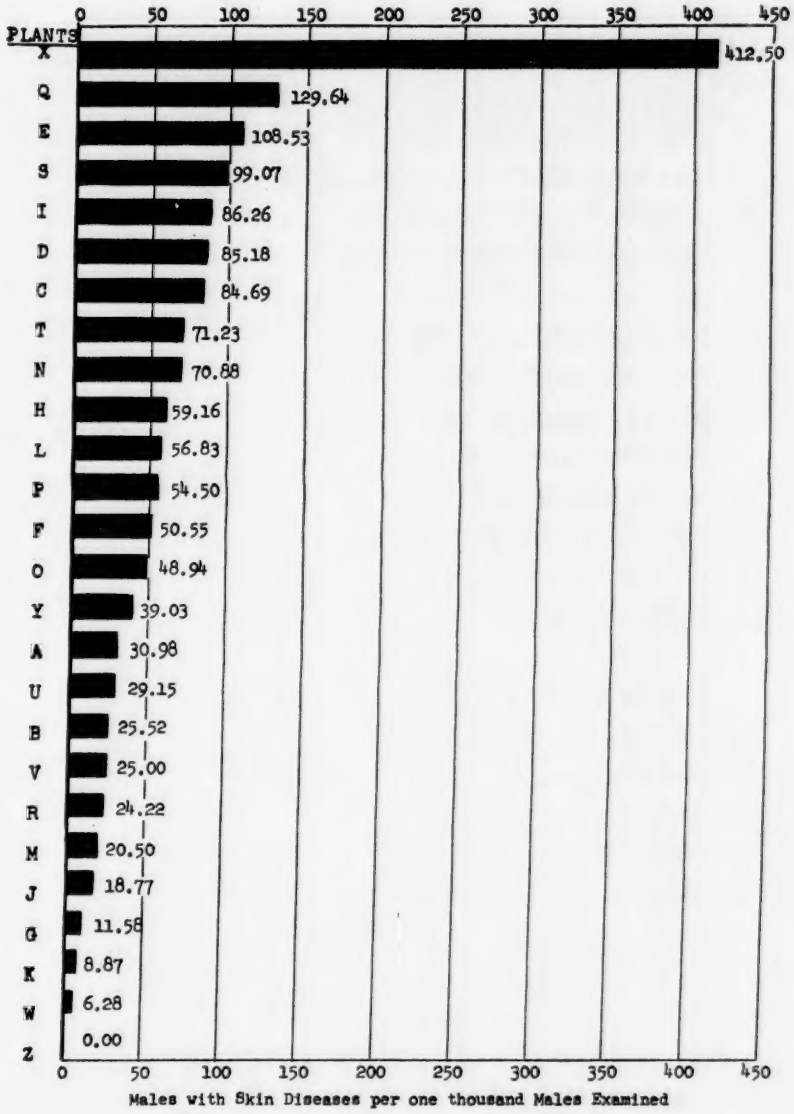

Fig. 2.—Prevalence (rates standardized for age to company age distribution) of skin diseases per 1,000 males examined by plants, 1952-1953.

factors influencing the development of disease among individuals free of the disease. In industry, the magnitude of a disease problem at any time is also influenced by the rate at which individuals who have the disease enter and leave the company and, for some diseases, the rate at which those who have the disease revert to the negative state.

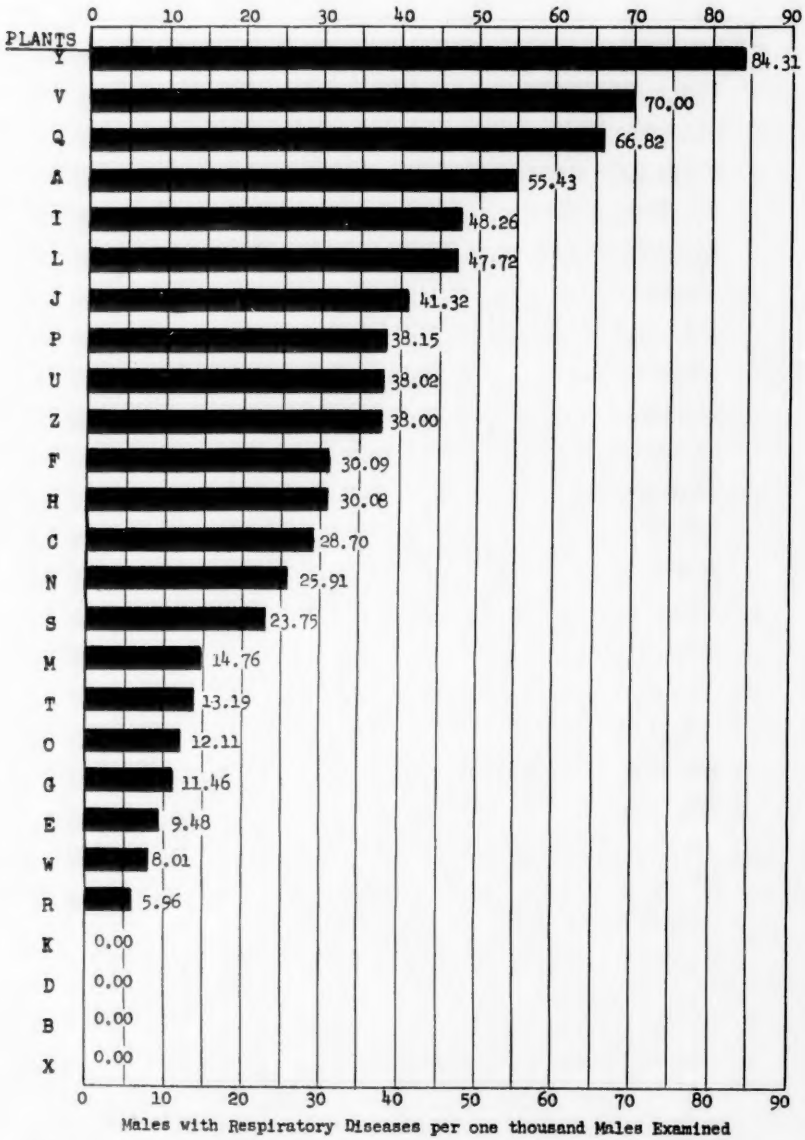

Fig. 3.—Prevalence (rates standardized for age to company age distribution) of respiratory diseases per 1,000 males examined by plants, 1952-1953.

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Knowledge of these rates not only helps to explain the prevalence observed at any particular time, but also could provide a tool for examining the factors influencing prevalence. Thus, the ability to determine the rate of development

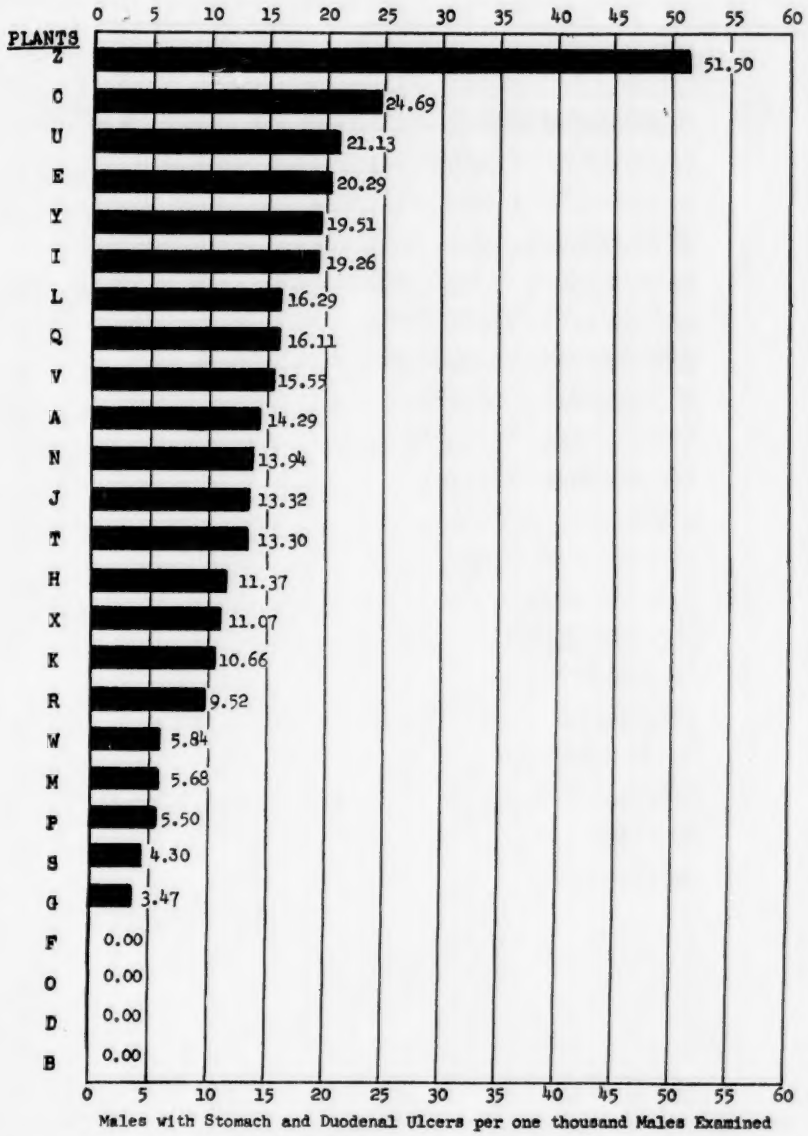

Fig. 4.—Prevalence (rates standardized for age to company age distribution) of stomach and duodenal ulcers per 1,000 males examined by plants, 1952-1953.

of hypertension permits examination of the question of whether an individual who is obese at the time of employment is more or less likely to develop hypertension than his fellow employee who was not overweight when employed.

An attempt was made to determine these rates for certain conditions among employees of Plants U, A, and I. The general procedure followed was to take all the individuals present in the punch-card file for a particular calendar year* and see how many were in the file in the next calendar year. The status with respect to the disease was noted for those individuals who could be traced.

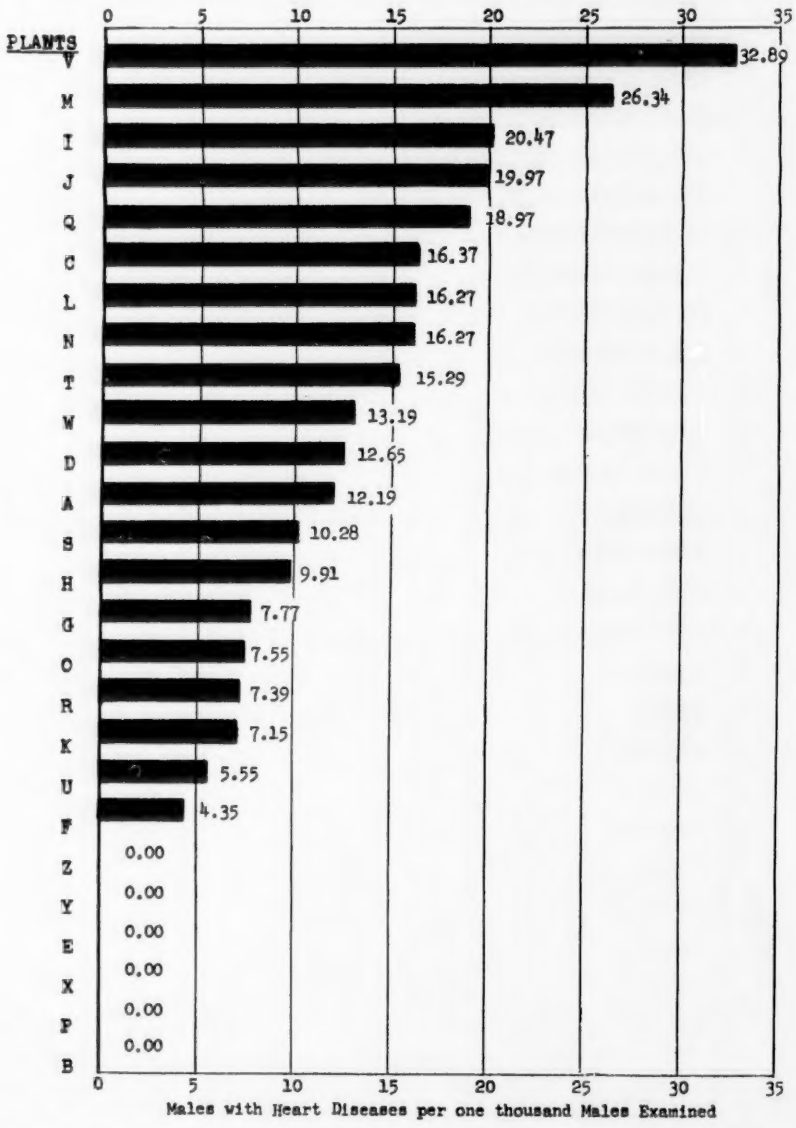

Fig. 5.—Prevalence (rates standardized for age to company age distribution) of heart diseases per 1,000 males examined by plants, 1952-1953.

*The calendar years used were 1946-1947 to 1947-1948 for Plant U, 1949-1950 to 1950-1951 or Plant A and Plant I.

The results of the analyses are shown in Tables I-IV. Referring to Table I, we see that the average annual rate of development of high blood pressure at Plant A (79.4 per cent) is over twelve times as high as at Plant U, while the rate

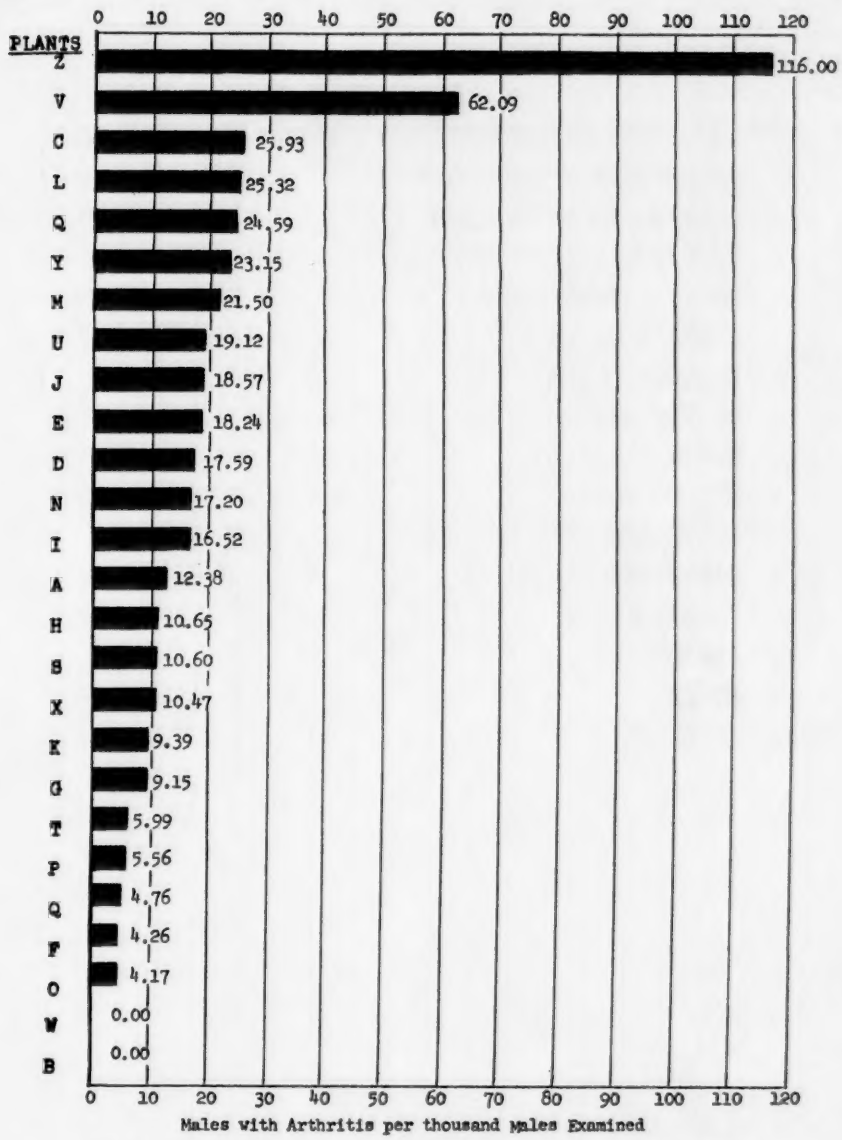

Fig. 6.—Prevalence (rates standardized for age to company age distribution) of arthritis per 1,000 males examined by plants, 1952-1953.

at Plant I is nearly ten times as high. When these rates are examined by age, they are all higher at the I plant and the A plant than at the U plant, in spite of the small numbers on which the rates for the individual age groups are based.

A similar degree of variation is noted in the rates of acquiring stomach and duodenal ulcers, heart disease, and arthritis.

When the data on the rate of reverting from positive to negative are examined (Table II), it appears that nearly two-thirds of the positives for high blood pressure at the U plant and the I plant revert back to negative, while at

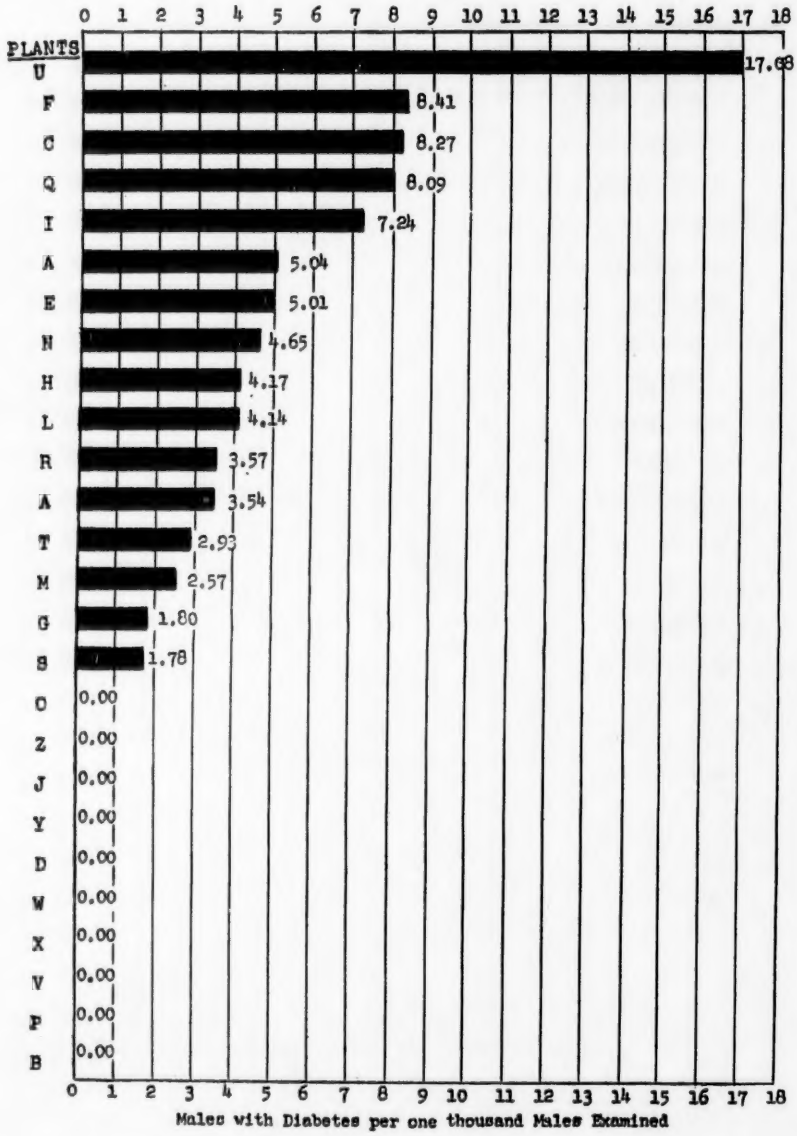

Fig. 7.—Prevalence (rates standardized for age to company age distribution) of diabetes per 1,000 males examined by plants, 1952-1953.

the A plant the figure is only one-quarter. Part of this high reversion rate is due to the definition of high blood pressure. For this analysis, which covers only two successive annual physical examinations, if a person had a blood pressure reading of 150 or greater systolic and 95 or greater diastolic, he was classed as having high blood pressure on that examination. Nevertheless, it is of interest

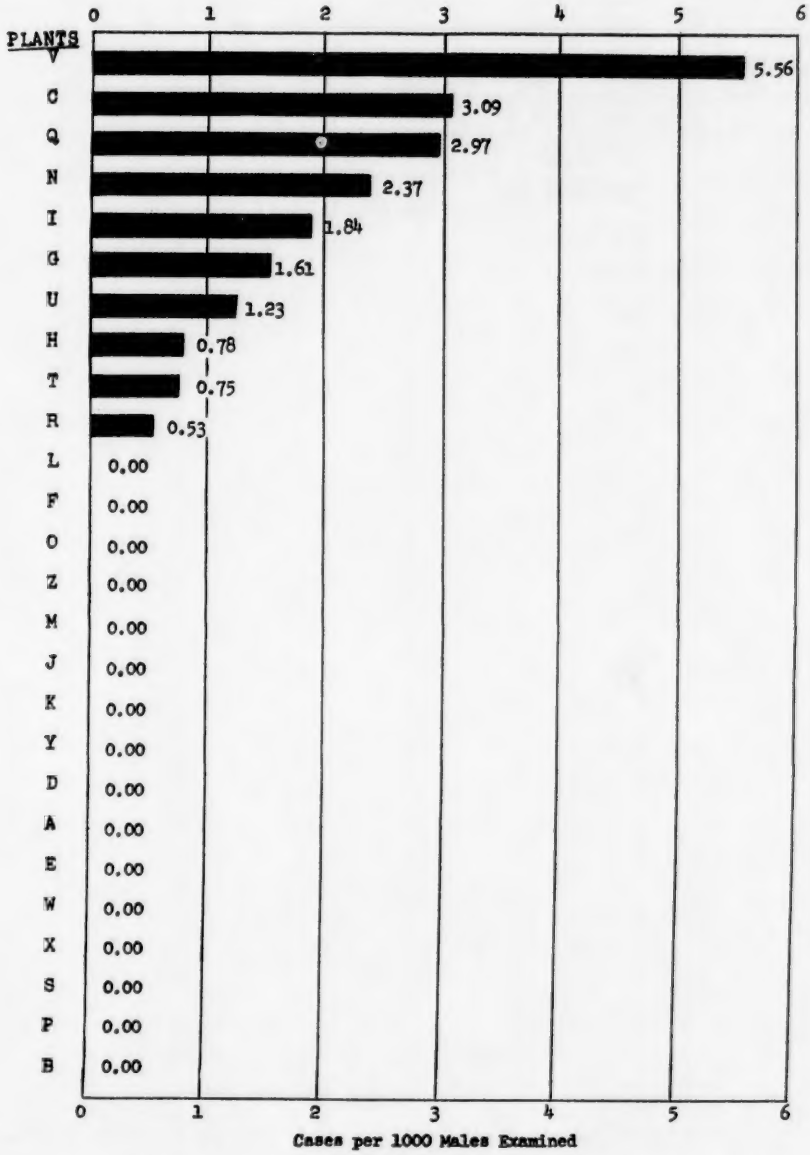

Fig. 8.—Plants ranked by frequency of cancer per 1,000 males examined, 1952-1953.

that in Plant A, with the high rate of acquiring high blood pressure, the reversion rate is low, while at U and I the reverse is true.

The reversion rates for stomach and duodenal ulcers are high at all three plants.

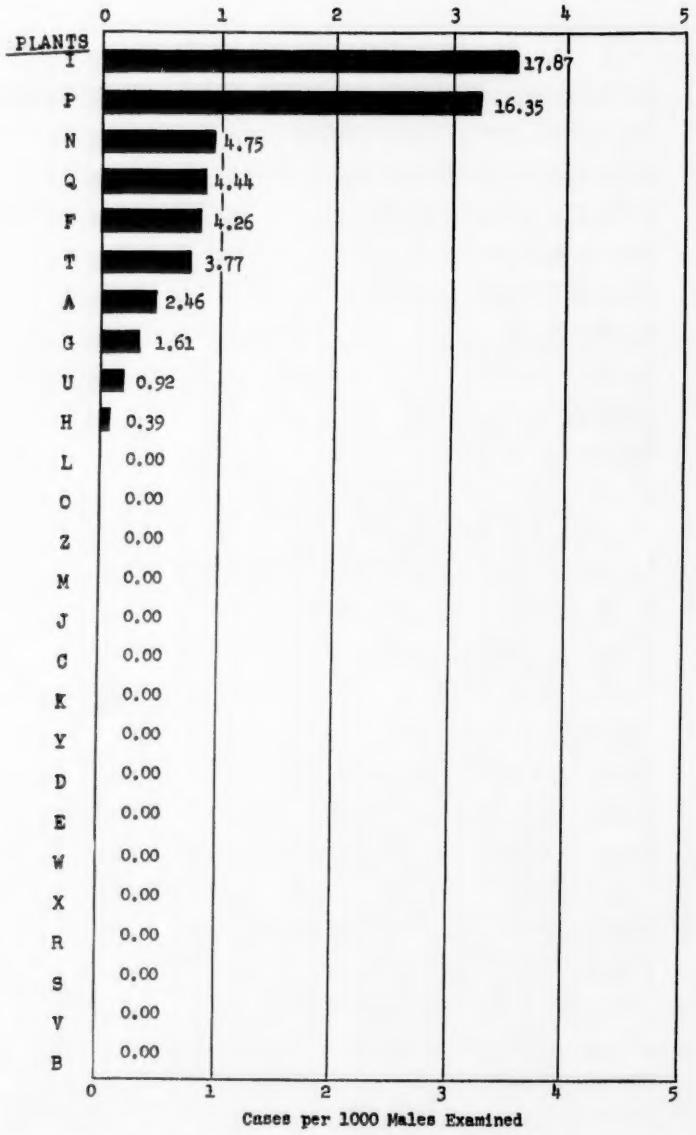

Fig. 9.—Plants ranked by frequency of disease of the blood and blood-making organs per 1,000 males examined, 1952-1953.

If employees who acquire a particular disease condition leave a company at a different rate than those who remain free of the condition, the plant population will tend to become more and more selected in nature. The type of selection will depend upon whether the positives leave at a higher or lower rate than the negatives. This point is examined in Table III.

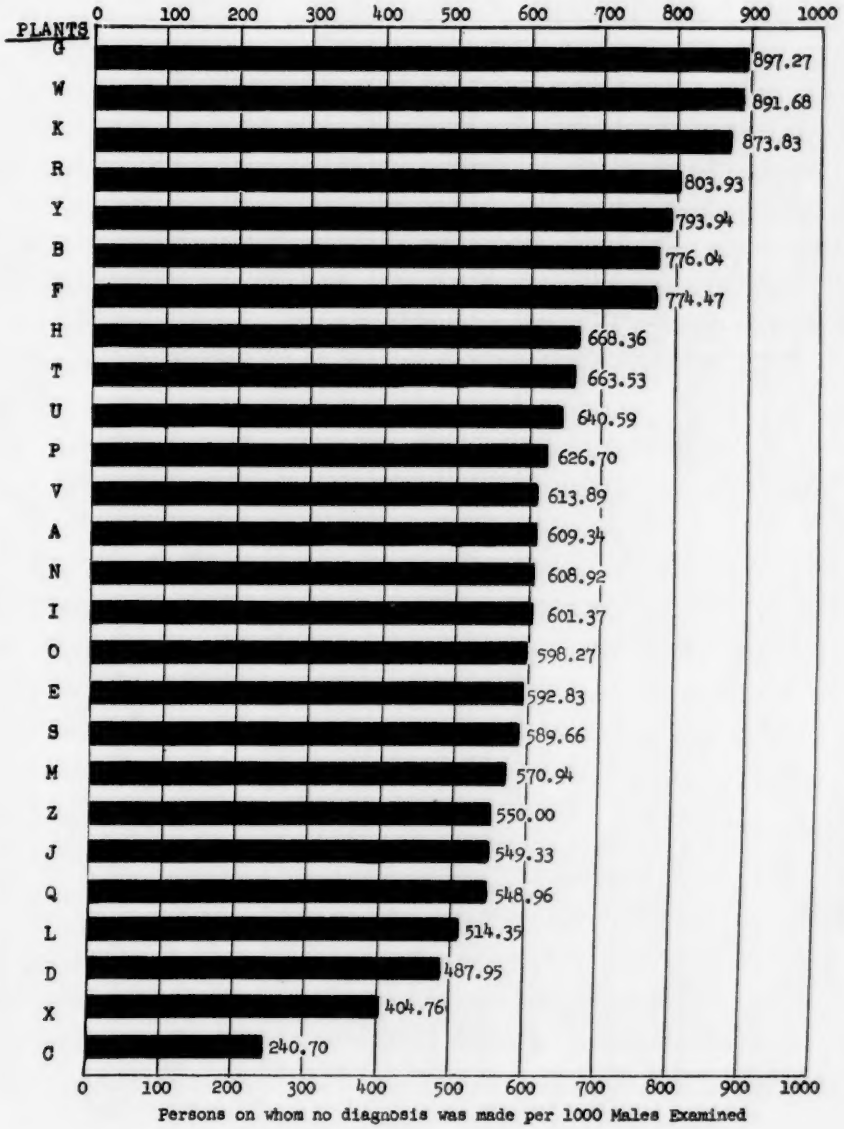

Fig. 10. —Plants ranked by frequency of males with no clinical diagnosis per 1,000 males examined, 1952-1953.

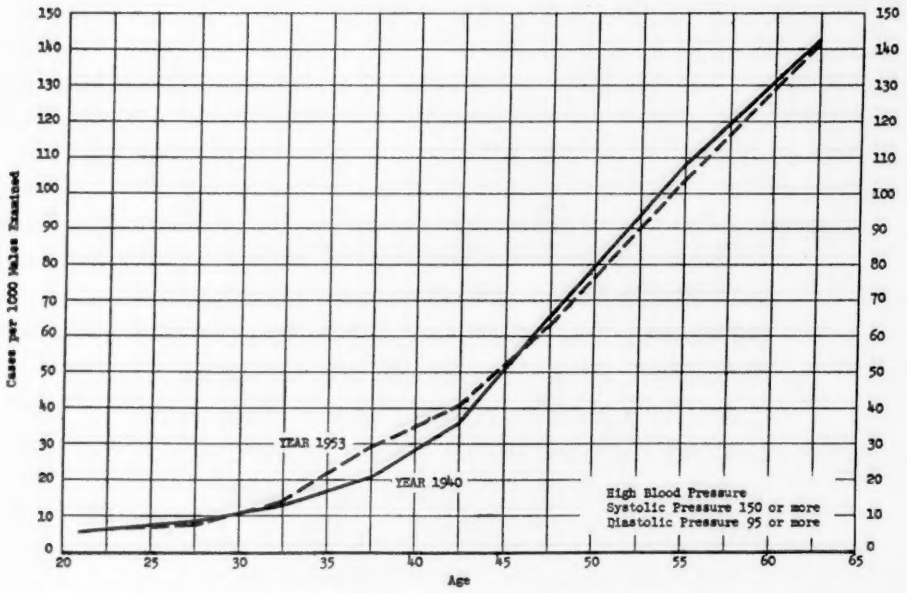

Fig. 11.—Relative frequency of high blood pressure (150/95 or more) per 1,000 males examined for twenty-six plants with records for the years 1940 and 1953.

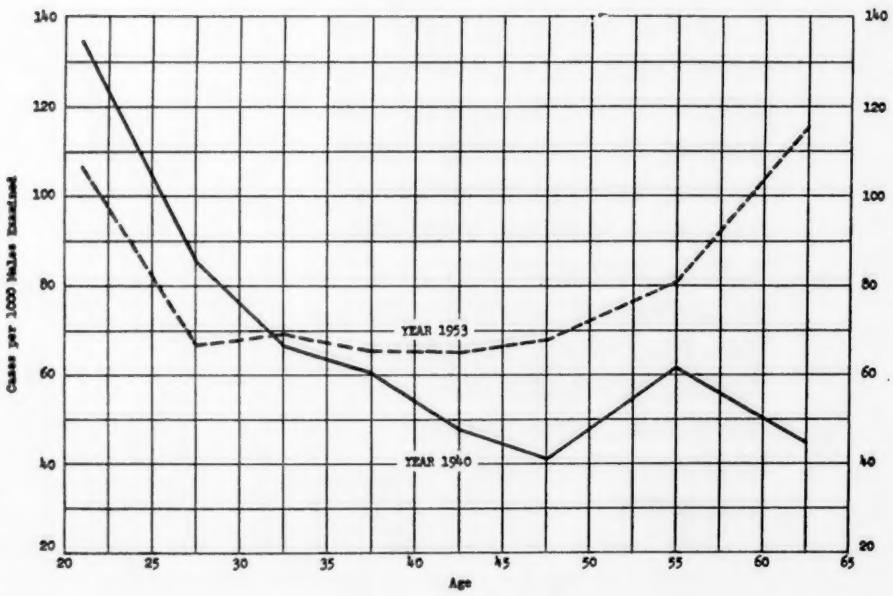

Fig. 12.—Relative frequency of skin diseases per 1,000 males examined for twenty-six plants with records for the years 1940 and 1953.

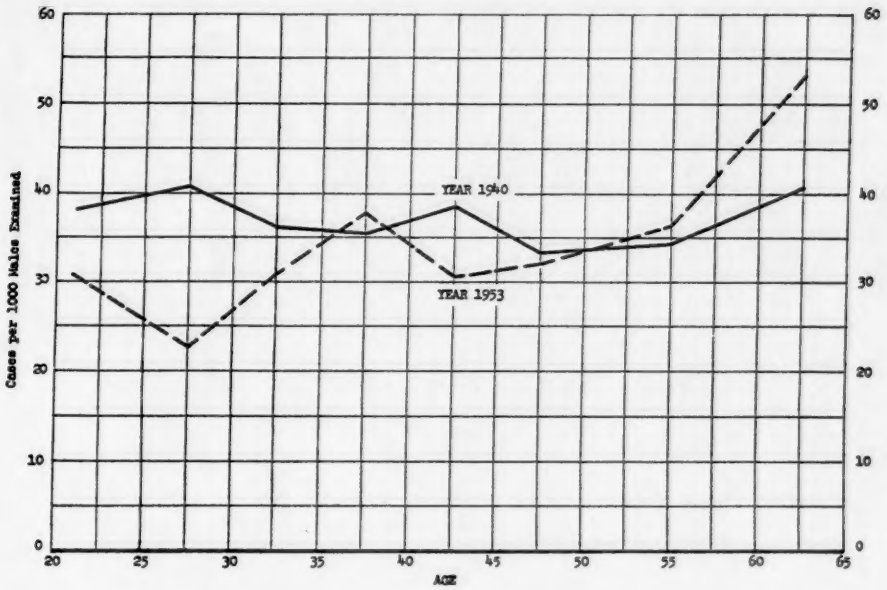

Fig. 13.—Relative frequency of respiratory diseases per 1,000 males examined for plants with records for the years 1940 and 1953.

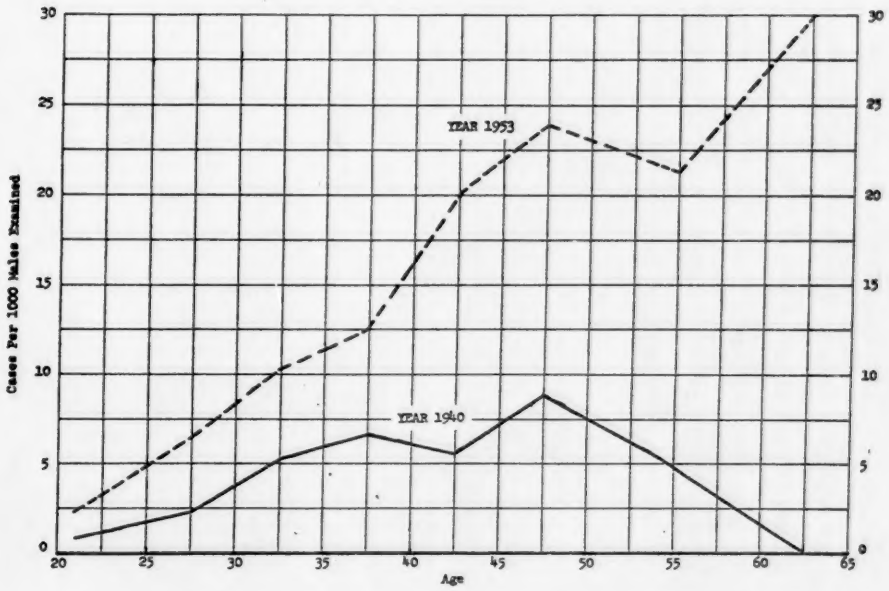

Fig. 14.—Relative frequency of stomach and duodenal ulcers per 1,000 males examined for plants with records for the years 1940 and 1953.

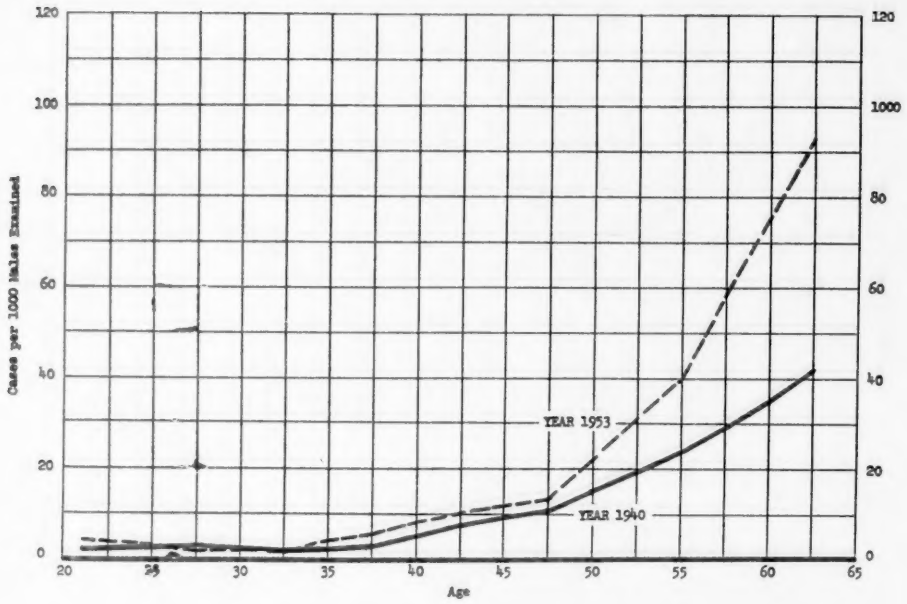

Fig. 15.—Relative frequency of heart disease per 1,000 males examined for twenty-six plants with records for the years 1940 and 1953.

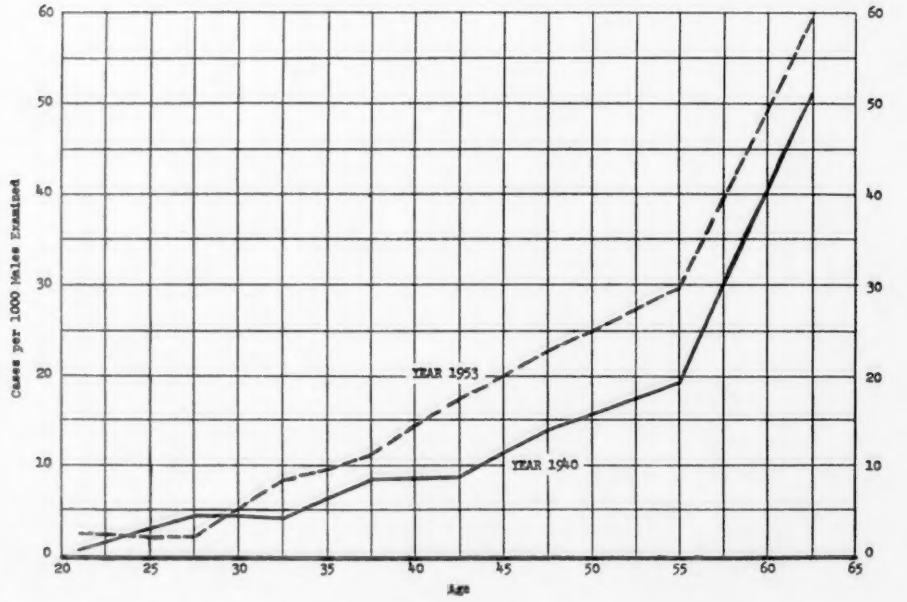

Fig. 16.—Relative frequency of arthritis per 1,000 males examined for twenty-six plants with records for the years 1940 and 1953.

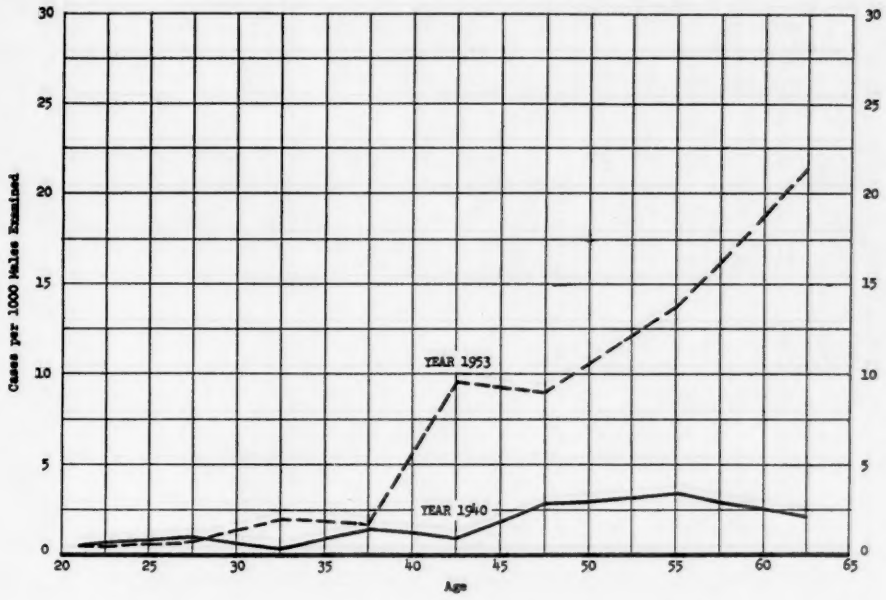

Fig. 17.—Relative frequency of diabetes per 1,000 males examined for plants with records for the years 1940 and 1953.

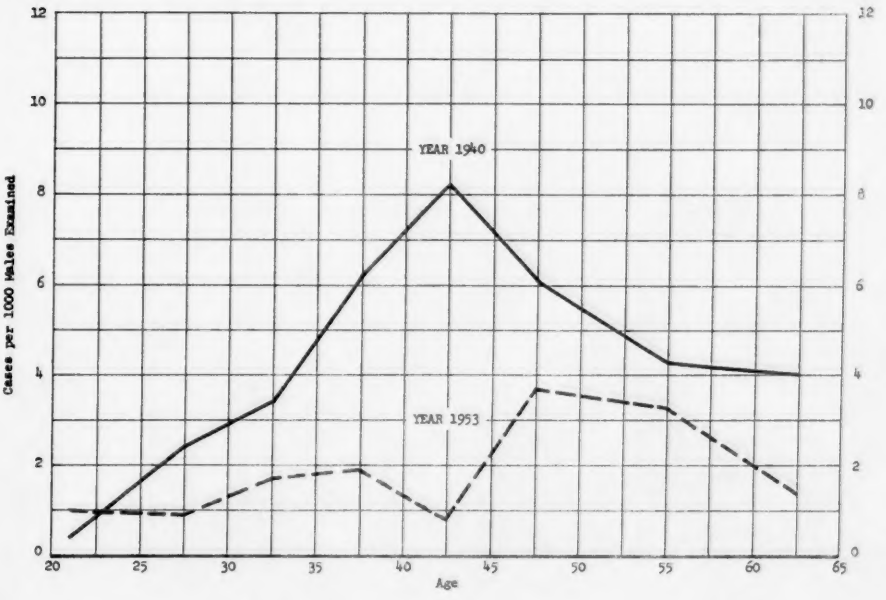

Fig. 18.—Relative frequency of syphilis per 1,000 males examined for plants with records for the years 1940 and 1953.

It is seen that the rate of loss to observation is about the same order of magnitude at Plants A and I. Both, however, have rates nearly twice those among the negatives at Plant U.

TABLE I. AVERAGE ANNUAL RATE OF ACQUIRING CERTAIN DISEASE CONDITIONS

CONDITION	RATE PER 1,000 MEN EXAMINED		
	PLANT U	PLANT A	PLANT I
High blood pressure	6.2	79.4	55.4
Peptic ulcers*	4.7	——	10.5
Heart disease	——	——	10.5
Arthritis and rheumatism	3.2	——	8.5

*Stomach and duodenal ulcers.

TABLE II. AVERAGE ANNUAL RATE OF REVERTING FROM POSITIVE TO NEGATIVE FOR CERTAIN DISEASE CONDITIONS

CONDITION	RATE PER 1,000 MEN EXAMINED		
	PLANT U	PLANT A	PLANT I
High blood pressure	639.3	250.0	658.5
Peptic ulcers*	933.3	750.0	965.5
Heart disease	†	†	800.0
Arthritis and rheumatism	842.1	†	823.5

*Stomach and duodenal ulcers.
†Too few observations on which to base rate.

TABLE III. AVERAGE ANNUAL RATE OF LOSS TO OBSERVATION*

CONDITION	RATE PER 1,000 MEN EXAMINED					
	PLANT U		PLANT A		PLANT I	
	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE
High blood pressure	247.7	306.8	475.0	625.0	473.2	485.4
Peptic ulcers†	248.9	285.7	485.6	——	474.1	420.0
Heart disease	248.3	625.0	483.1	714.3	473.3	487.2
Arthritis and rheumatism	249.3	208.3	488.3	428.6	472.2	595.2

*An individual may be lost to observation either because he leaves the Company, or because there is no record of his having had an annual physical examination in the calendar year being studied.
†Stomach and duodenal ulcers.

TABLE IV. RATIO OF NEW TO OLD EMPLOYEES* BY DISEASE STATUS AT TIME OF EMPLOYMENT

CONDITION	PLANT U		PLANT A		PLANT I	
	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE
High blood pressure	361.5	189.2	81.1	—	251.0	57.5
Peptic ulcers†	358.6	105.3	75.8	—	240.0	20.4
Heart disease	357.9	—	75.4	—	239.1	26.3
Arthritis and rheumatism	360.0	—	75.4	—	239.4	23.8

*Per 1,000 old employees.
†Stomach and duodenal ulcers.

Employees who develop high blood pressure or heart disease at Plant U or A are lost to observation at a higher rate than those remaining free of these conditions. The loss is greater for heart disease than for high blood pressure. Furthermore, the ratio of the losses among positives to those among negatives is about the same at both locations. At Plant I, however, there is very little difference between the loss rates of positives and negatives. It is probable that a part of this loss may be interpreted as persons actually leaving the company. Thus at U and A the employee population remaining with the company tends to be selected in favor of those remaining free of the condition.

In contrast to the two conditions just discussed, there is very little difference in the loss rate of positives and negatives with respect to ulcers or arthritis at any of the three plants, at least when all ages are considered together. The numbers in the individual age groups become too small to see if there is any trend with age.

The employed population tends to become selected in favor of those remaining free of the disease in still another way. As would be expected, a greater proportion of negatives are hired than positives. This is seen in Table IV. It may also be noted that this goes on at a greater rate at Plants U and I, than at the A plant.

DISCUSSION

The outstanding fact brought out by the foregoing analyses is that whether we are concerned with the static situation represented by the prevalence of a particular disease condition at some point in time or the dynamics which result in the observed prevalence, there is great variation among the different plants of the Company.

The meaning of this variation is not clear at this time. It is worth while, however, to consider the various ways in which the differences among the plants might come about and their implications if true.

If the observed differences among the plants reflect real differences in the amount of disease present in these plants and in the rate at which it develops, the possibility that such differences are occupational in origin should be given

very serious attention. Thus, if one plant *really* has twelve times as much hypertension or peptic ulcer or some other condition as another, detailed medical and engineering studies would be indicated. However, before such elaborate investigations are undertaken it would be well to examine other hypotheses concerning the observed variation.

It is possible that the observed variation may primarily reflect differences in examining procedures* in the different plants, better methods of diagnosis in more recent years, differences in recording procedures, variations in completeness of reporting to the central office. Indeed, there is evidence within the material itself that this is a more likely hypothesis than that suggested in the preceding paragraph.

For example, Plants Z, Y, and V, which are explosives' manufacturing plants, have a program of screening of hypertensive persons because of the environmental hazards of the plants. Their prevalence rates in 1952-1953 were low (Fig. 1). On the other hand, Plant O has a prevalence of hypertension in the middle range (38.74) while Plant V has the highest heart disease rate. These two plants also make explosives. It would appear, therefore, that factors other than the type of manufacturing process produce the observed variation.

A similar situation exists with respect to certain plants that manufacture chemicals which are skin irritants. Such plants as X, Q, E, and S have a high rate of skin diseases, while U and J, in which employees have equal opportunity for contact with chemicals, have a relatively low prevalence of such conditions.

Thus, the internal evidence of the data themselves suggests that the factors responsible for the observed variation are due to local conditions other than those associated with occupations common to explosives plants or synthetic fibers plants.

The data on the age-specific prevalence rates in the two time periods also contain some indications that the observed increases with time do not necessarily represent an actual increased amount of disease among employees. It has been noted previously that the prevalence of high blood pressure by age had not changed notably between 1940-1941 and 1952-1953. In contrast to the quantitative observation of blood pressure obtained by an ostensibly standard procedure, we have the observation on gastric and duodenal ulcer. The increase in the latter condition shown in Fig. 14 is tremendous. In the period studied there may also have been an increased use of the x-ray film as a diagnostic aid. If so, this would tend to increase the interest and the awareness of the physician in this condition, resulting in more frequent case finding and an increase in recording of the disease.

A similar sequence of events may have taken place for the other diseases for which increases have been shown.

Which of the two broad general hypotheses suggested is correct—that the observed variation in prevalence is real or that it is the result of differences in examining procedures or other techniques—cannot be determined without further

*In the duPont Corporation the medical department of each plant is autonomous although general supervision is exercised by the Wilmington office. Specific examining and recording procedures may, therefore, be developed differently in different plants.

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facts. Since there is a suggestion in the data that the second of the two hypotheses is the more probable one, the conclusion is reached that a more detailed investigation into examining procedures, recording practices, reporting procedures is warranted.

This conclusion has significance for industry generally as well as for the particular company represented by the data. There are two reasons for this: (1) In an unpublished analysis* of absenteeism and dispensary visits among the various plants of another major chemical company, wide variations were observed in the rates among the plants. Moreover, as in the present study, there were indications in the data themselves that much of the variation probably did not represent any real variation in the risk of being ill but rather was the result of differing practices both medical and administrative. Thus, the need to identify and understand this variation may transcend individual companies or even individual industries. (2) In view of the practical uses to which knowledge of the extent of particular diseases in industry may be put—some of which have been indicated in the opening paragraph of this paper—it is important to know just how widespread this phenomenon of variation is. If it is confined to the chemical industry, the problem is quite different from that which would be the case if such variation is found in industry generally. A better understanding of the extent and nature of this variation is essential if the practical problems cited are to be dealt with on a rational basis.

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SUMMARY

1. Whether the potential value of the pre-employment and periodic physical examination in adding to knowledge of chronic disease can be realized is dependent upon whether the observations made on the individual employee are, or can be, recorded and organized in such a way as to (a) delineate the dimensions of the problem among employees *as a group* and (b) identify the factors influencing the size of the problem.

2. The purpose of this paper has been to examine the feasibility of achieving these objectives with data available from the employment and periodic physical examinations of employees of the E. I. duPont de Nemours Company.

3. The prevalence of high blood pressure, skin diseases, respiratory diseases, heart disease, arthritis, diabetes, cancer, and diseases of the blood and blood-making organs was examined among employees in the different plants of the Company.

4. The most striking feature of the prevalence was the tremendous amount of variation found in the rates for different plants. This variation was not confined to specific diagnoses. There was also great variation in the frequency with which *any* diagnoses were made.

5. In addition to great variations in prevalence of chronic diseases among the plants at a particular time, there were also wide variations over a period of time in the apparent prevalence of certain conditions in the group of plants.

*This analysis was conducted by the Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh.

6. Two broad hypotheses to explain this variation are suggested: (a) that the observed variation in prevalence is real or (b) that it is the result of differences in examining procedures or other techniques. There is a suggestion in the data that the second of the two hypotheses is the more probable.

7. The conclusion is reached that a more detailed investigation into examining procedures, recording practices, and reporting procedures is warranted.

8. This conclusion has significance for industry generally because (a) similar wide variations were observed among the plants of another major chemical company and (b) the practical uses of knowledge of the extent of particular diseases in industry make it important to know just how widespread this phenomenon of variation is. If it is confined to the chemical industry, the problem is different from that which would be the case if such variation is found in industry generally. One cannot deal with these practical problems without a better understanding of the extent and nature of this variation.

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THE PRESENT-DAY MANAGEMENT OF ARTHRITIS

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(Received for publication Oct. 11, 1954.)

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INTRODUCTION

The title of this paper is consistent with the progress achieved in the study of rheumatism in the past three decades. During this period, concrete advances have been made in our understanding of these diseases, and several phases of predominant interest have been pursued. It seems fitting to discuss arthritis management in the chronological order which has evolved. The use of the term "management" rather than "cure" or "treatment" also conforms with historical concept. "Cure" was used extensively in titles in the twenties and thirties, "treatment" in the forties, and, in the last few years, the term "management" has been widely invoked. With advancing knowledge of the disease states under discussion, we have come to realize that we "cure" very few; that "treatment" implies a passive role on the part of the patient; whereas "management" requires his active cooperation, with the physician acting in an advisory or guiding role.

DIFFERENTIAL DIAGNOSIS

During the past thirty years, an early, lasting contribution to our knowledge was the differentiation of rheumatoid arthritis from degenerative joint disease, with the abandonment of the term "mixed arthritis." Gout and true infectious arthritis of microbial origin had been recognized as separate entities before this. Each of these distinctions had been brought about by the application of new tools of differential diagnosis—the uric acid blood level, methods for the culture of microorganisms, and the erythrocyte sedimentation rate. Clinical and pathologic appraisals had given excellent recordings of each typical disease pattern, but for general application to the mass of patients, a simple diagnostic test was necessary. Classification of the rheumatic diseases and separation into different entities continue to provide a fertile field for clinical investigation.

Supported in part by a grant from the Masonic Foundation for Medical Research and Human Welfare.

Read at the First Interstate Scientific Assembly, Washington, D. C., Nov. 2, 1954.

The recent application of the test for the L.E. phenomenon of Hargraves[1] to a wide clinical spectrum has evidently been one factor in the apparent increasing incidence of disseminated lupus erythematosus. The specificity of this procedure, suitably performed, seems to be high, but only time and continued clinical and pathologic correlations can provide the final index of its true reliability.

The differential diagnosis of the various rheumatic diseases continues to be the first task of the physician who is faced with the problem of management. Almost every therapeutic tool at his disposal has potentialities for harm and should not be utilized unless indicated. The indications for a particular form of treatment depend primarily upon accurate diagnosis and demand consideration of prognosis as to duration of life, and as to possible crippling and future derangement of economic and social life. The immediate future of an hour, a day, or a month is relatively unimportant, overshadowed by the future in terms of years. *The long-term viewpoint is essential in the management of arthritis.*

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The differential diagnosis of the rheumatic diseases, as the first step in management, is not easy, particularly in their early stages. In the absence of evidence of inflammation, notably an elevated erythrocyte sedimentation rate, it is frequently impossible promptly to make up one's mind. In this case, patience is essential on both sides of the doctor-patient relationship, and a clear-cut explanation to the patient of the advantages of watchful waiting is necessary. Our practice has been to employ mild antiphlogistic agents such as salicylates to, but not beyond, tolerance during this phase, to attempt to know the patient as completely as possible, and to modify his life situation slightly toward more rest.

Fibrositis, which is generally thought[2] to represent a reaction to an environmental situation, may be used as an example. This symptom pattern may also represent the onset of rheumatoid arthritis or of disseminated lupus. We are unable to see how a period of watchful waiting is deleterious in this situation. By withholding drastic therapeutic measures, the possible introduction of iatrogenic disease may be avoided.

If evidence of inflammation is present, the problem becomes more urgent and complex. When joint involvement is monarticular, one must consider microbial involvement, either pyogenic or tuberculous, and a philosophy of watchful waiting may well be harmful. Especially in children with tuberculous arthritis, speed is essential since a much more favorable prognosis has resulted from the early use of suitable antibiotics. Our policy in the presence of a positive tuberculin reaction in a child with a single inflamed joint has been to exclude rapidly a pyogenic infection by a three-day course of penicillin, rigidly avoiding streptomycin, which would only confuse the picture. Since cultural and particularly animal inoculation methods of isolation of the tubercle bacillus take weeks, we resort to biopsy for diagnosis. Since tuberculous synovial involvement may be spotty, we prefer to carry this out under direct observation with full exposure rather than by a punch technique. We feel that a rapid exhibition of suitable therapy in tuberculous arthritis outweighs the disadvantages of an open joint.

In the adult, clues to the diagnosis of monarticular arthritis depend upon sex: gout is rare in females; upon age: gout is uncommon before 30; and upon evidences of disease elsewhere. Since, in our experience, first attacks of gout may occur with a borderline serum uric acid, we frequently follow a standard procedure in acute inflammatory monarticular arthritis in the adult. We tap the joint in a search for microorganisms by smear and culture. Regardless of the result and immediately after the diagnostic tap, 1 to 2 million units of long-acting intramuscular penicillin is given daily for three days, primarily because early treatment of a pyogenic joint is essential to prevent cartilaginous destruction and is specifically curative. If the response is not dramatic, a therapeutic trial of colchicine is used (1 mg. every two hours for five doses, or to stop with the onset of diarrhea). If the response to two courses of colchicine is nil, we then start with salicylate as therapy on the assumption that we are probably dealing with atypical rheumatoid arthritis, rheumatic fever, or disseminated lupus erythematosus. Occasionally, acute arthritis resulting from degenerative joint disease will develop and may be confused with either gout or a pyogenic joint, but in most instances, there is a story of trauma preceding the acute onset and the inflammation is rarely so intense as to make this differentiation necessary.

When the arthritis involves multiple joints with an acute onset, one must consider rheumatic fever as a first choice. We feel that withholding salicylates in this situation is seldom indicated. This opinion is based primarily upon Fischel's[3] hypothesis that salicylates may have an anti-inflammatory action on myocardial inflammation as well as on the inflammation present in the joints. The arthritis of rheumatic fever only rarely fails to respond to salicylates. With a complete response, we proceed on the assumption that we are dealing with rheumatic fever and observe the patient essentially from the point of view of his heart, using all the usual means to detect deviations from the normal. Salicylates are continued for periods of time which may seem overlong to many, usually for one month after the erythrocyte sedimentation rate returns to a normal range, to avoid, if possible, a withdrawal rebound. One must always keep in mind the possibility that an acute multiple arthritis may represent the initial episode in rheumatoid arthritis or disseminated lupus. On the basis of probability, however, in an adolescent or young adult, rheumatic fever should first be considered.

So much for the acute problem faced in the management of arthritis. Only the most common situations have been discussed but one must remember that many diseases seen on a medical ward may at some time in their course have joint manifestations of greater or lesser intensity. The list given in Table I covers a few of these but not all.

In chronic disease, the differential diagnosis is also intimately connected with management. The group of patients exhibiting the symptoms and signs of rheumatoid arthritis must be distinguished in the main from those with degenerative joint disease, one or other of the collagen diseases, or protracted rheumatic fever. In degenerative joint disease, evidence of inflammation is scanty or absent. The collagen diseases, particularly disseminated lupus and allergic angiitis, or periarteritis nodosa, usually present clinical evidence of wide-

spread disease. A positive L.E. phenomenon is a characteristic diagnostic finding in the first of these entities. In a few patients with early scleroderma or dermatomyositis, the clinical findings may mimic those of rheumatoid arthritis. The sickness pattern of some patients with chronic rheumatic fever is similar to that seen in rheumatoid arthritis. In rheumatic fever, however, the onset follows an upper respiratory infection due to the hemolytic streptococcus; the response of the arthritis to salicylates may be more complete; the antistreptolysin-O titer is elevated more frequently than in rheumatoid arthritis, and evidence of rheumatic carditis by auscultation or electrocardiography may be obtained. In all these situations, if no specific evidence for one particular disease exists, and it frequently does not, the only course to pursue is that outlined for the patient without evidence for inflammation, namely, watchful waiting during adequate administration of salicylates, time to know the patient, and appropriate restriction of activity. Our experience indicates that this period of waiting does little harm, minimizes the chances for unnecessary iatrogenic disease, and most important of all, it allows the patient to have a spontaneous remission if that is the nature of the particular bout under observation.

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TABLE I. SYNDROMES WHICH MUST BE DISTINGUISHED FROM RHEUMATOID ARTHRITIS SINCE EACH HAS, IN OUR EXPERIENCE, BEEN CALLED RHEUMATOID ARTHRITIS

Degenerative joint disease	
Rheumatic fever	
Lupus erythematosus disseminatus	
Periarteritis nodosa	
Scleroderma	
Fibrositis	
Pyogenic arthritis	
Tuberculous arthritis	
Gout	
Shoulder-hand syndrome	
Hypertrophic pulmonary osteoarthropathy	
Multiple myeloma with or without amyloid	
Hemophilic arthritis	
Boeck's sarcoid	
Sudeck's atrophy	
Reiter's syndrome	
Leukemia	
Iatrogenic arthritis	
Ochronosis	
Neurological disorders:	cord tumors
	tabes dorsalis
	syringomyelia
	amyotrophic lateral sclerosis

Unfortunately there is no diagnostic test specific for rheumatoid arthritis. We usually arrive at a diagnosis of rheumatoid arthritis by exclusion after going through the usual categorizing procedures of differential diagnosis. The typical

patient should have the characteristics outlined in Table II, but in the early phases of the disease at least one-third do not. It is common for an atypical onset to be followed by the classical picture of rheumatoid arthritis after the passage of months or even years. Diagnosis by exclusion, although necessary, is an unsatisfactory procedure and has been and continues to be a great stumbling block in the study of this disease. The serologic reactions seen in rheumatoid arthritis[4] are fairly specific (that is, false positives are rare), but many with the disease do not have the agglutinating factor, and these tests are frequently positive in disseminated lupus. The newer modifications of these reactions (hemagglutination)[5] are being studied intensively but are difficult to perform, and when the sensitivity of the tests is raised to increase the number of positives in patients with rheumatoid arthritis, the number of false positives may also be increased. The number of positives increases with the duration and/or severity of the disease, and the reactions are most commonly positive in the typical patient where the diagnosis is obvious. Although our clinic is enthusiastic in the study of these serologic reactions to unravel the mysteries surrounding pathogenesis, we are not enthusiastic about their use as diagnostic tools. Their chief value is to offer confirmatory evidence.

TABLE II. FINDINGS COMPATIBLE WITH A DIAGNOSIS OF RHEUMATOID ARTHRITIS

1. Typical symmetrical involvement, particularly including wrists and proximal interphalangeal joints, with stiffness after inactivity (gelling)
2. Persistence of (1) for 6 months at least
3. Elevated erythrocyte sedimentation rate
4. X-ray changes of generalized and localized demineralization, loss of joint space, and punched-out areas near the joint space
5. Juxta-articular nodules
6. Positive streptococcus or sensitized sheep cell agglutination

Under most instances, a patient exhibiting the above findings has rheumatoid arthritis. This is particularly so if the individual is a woman between 25 and 40 years of age.

THE NATURAL HISTORY OF RHEUMATOID ARTHRITIS

Following the original work on classification of rheumatoid arthritis, the advances of the 1940's concerned the delineation of its natural history. By the very nature of the material dealt with, human subjects, the course of rheumatoid arthritis has rarely been studied in its natural state because aspirin can be obtained without prescription and is commonly used by patients long before they consult the physician. There have been, however, large groups of patients studied with one type of therapy or another predominating and these groups have been compared with each other. Two major difficulties have limited the value of these investigations. The first revolves about our difficulty in deciding precisely when rheumatoid arthritis exists. The work of Cobb and his associates[6] in Pittsburgh has highlighted this problem. During an epidemiologic study in a city health district, they found that many people exhibited the symptom complex of stiffness after inactivity with varying degrees of joint inflammation.

These individuals seldom seek medical assistance and, in the study, great difficulty was experienced in classifying the patient with atypical disease. In our own long-term study[7] we were impressed with the frequency with which a patient with typical rheumatoid arthritis gave a story of an abortive attack of arthritis lasting two, four, or ten weeks, five to ten years before the onset of typical sustained disease. Short and Bauer[8] have stressed the variability of the disease in the group they studied. Four main types have been noted,[9] only one of which exhibits sustained progressive disease. These factors all combine to highlight the difficulty pointed out by Cobb and his group.

The relationship between diagnostic criteria and therapeutic evaluation may be compared to the shutter of a camera and the image photographed. If the shutter is stopped to a small aperture and rigid diagnostic criteria are employed whereby typical, far-advanced cases only are included, the evaluation of therapy will be nihilistic. If the shutter is wide open, and a broad-minded approach to diagnosis is employed, early, atypical, and equivocal cases are included. The therapeutic evaluation will then be an optimistic one since many spontaneous remissions will be attributed to the particular form of therapy being tested.

The second enigma raised in the study of rheumatoid arthritis is the difficulty associated with efforts to make an adequate assessment of the end result. The classification of progression of disease and of response to therapy adopted by the American Rheumatism Association[10] is difficult to follow and, since the advent of cortisone, needs and is undergoing revision. The intensity of the disease waxes and wanes; every evaluation must be classed as of the day the evaluation was made. The end results used in various published reports have constituted an attempt in the direction of objectivity but have included large amounts of the patients' subjective responses as well. The work or functional capacity of a patient is hardly a fair end point, particularly when the recently emphasized question of motivation arises to plague the physician (and his associates) who attempt to assess such factors. The activity of the disease is in large part a statement of the patient's symptoms colored by the feelings of the physician during his appraisal of the clinical state. The doctor's memory is short and must depend on prior evaluation recorded in notes. It must not be forgotten that shortly after the dramatic motion picture made by Hench demonstrating the beneficial effects of cortisone in rheumatoid arthritis, some equally dramatic films were produced to prove the beneficial effects of pregnenolone, an agent which all observers relegated to the wastebasket four years after its introduction. The objectivity found in evaluating cancer statistics, say the five-year survival rate, is at the present time far beyond the capacities of the physician in the field of the rheumatic diseases. Thus, to place the study of the natural history of rheumatoid arthritis (and as a corollary to this, the evaluation of therapy) on a sound level, three needs are apparent: a simple specific diagnostic test, uniform diagnostic criteria, and a method for evaluating progression of the disease.

MANAGEMENT OF RHEUMATOID ARTHRITIS

With these preliminary and somewhat deprecatory comments as a preface, one approaches a discussion of the management of rheumatoid arthritis with

some trepidation. This preface is necessary to avoid a doctrinaire approach to management and to develop an alertness to the inconsistencies found in the medical literature concerning remedies advocated for the management of this disease.

In the first place, no means are at hand to terminate the disease directly. There are two physiologic approaches to the management of the disorder. These are the indirect measures of physical medicine (based on sound premises) and the anti-inflammatory agents (based in hindsight on their antiphlogistic properties). The logical concepts involve rest since one may assume that an inflamed part will do better with more rest. The remainder of management represents pure empiricism which may ultimately be explained on a sound basis but which up to now has evolved from trial and error using the patient as the experimental object. The advances in the last decade have centered about those measures for symptom control which have a physiologic basis. The great majority of these measures have been introduced in human disease, and their rationale has subsequently been explained by translating the human disease to models of inflammation artificially produced in animals but in no sense mirroring the human disease.

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Thus, utilizing rational, logical, and empirical measures, the management of rheumatoid arthritis may be approached with three general principles in mind: (1) The long-term viewpoint; (2) pain relief; and (3) palliation in late disease. These three principles will be discussed in detail.

1. *The Long-term Viewpoint.*—When dealing with a chronic rheumatic problem, one is faced with the difficulties encountered in the course of any chronic illness of unknown causation, and remarks made in this vein would apply to other disease states as well as to rheumatoid arthritis. The first point to be made is that one does not treat symptoms blindly. True, the patient demands relief and rightly so, but few patients will continue to be unreasonably demanding if the long-term viewpoint is explained to them. A classic example of this is the pillow beneath the knee to ease the pain, which is guaranteed to upset the consultant and provide fuel for his flames of righteous indignation concerning the development of flexion contractures. Another example is the use of cortisone or hydrocortisone in the patient with early or mild disease. This is like shooting a large-bore cannon to bring down a chicken hawk.

Rheumatoid arthritis is an example of a disease of unknown etiology in which the psychosomatic approach has secured a beachhead. With advancing knowledge, certain previously accepted organic disorders, notably paresis and pellagra, have been eliminated from the psychiatric sphere. It is possible that rheumatoid arthritis will join the group of diseases seceding from the psychosomatic group or it may become more firmly entrenched in that area. At present, one cannot predict which way knowledge will lead us. The point to be emphasized at this writing is that an attitude of agnosticism is preferable regarding this particular conflict since the proponents of neither side have concrete evidence for their arguments. For this reason, one may not completely exclude environmental influences as a potential irritant in this disease, nor can one go to the other extreme and conclude that psychoanalysis must be the sole form of control. We

are reasonably certain that situational influences may lead to remissions and exacerbations. We do not feel as strongly as do some that the initial phases of the disease may be mediated through the emotional route. One feature stands out which is worthy of mention. Many of these patients have deep-seated anxieties which they find difficult to discuss. As an example: A patient had an acute episode of rheumatoid arthritis lasting one year from which she made a complete recovery. At the end of a five-year remission, she had a subsequent relapse while in conflict with her daughter. Only at this time did she relate that the original episode occurred at a time she was violently in dispute with her husband. In both attacks, resolution of her problems took place at the time of her remission, the first after 1 Gm. of gold compound, the second after 550 mg.

In any event, these problems are often not only too intangible to define but are also frequently insoluble. We feel, however, that the management of rheumatoid arthritis requires a complete rapport between patient and physician with honesty paramount on both sides. This cannot be achieved quickly, but it needs no special skill or board certification. It requires only time and a desire on the part of the physician to do the best possible job. In our experience, this is the function of the family physician and not the psychiatrist, since in most instances, when referred for psychiatric evaluation, our patients have been returned to us, as they were considered to be too fixed in their problems to be responsive to formal psychotherapy. Psychiatrists rarely have time to tackle the great bulk of individuals with rheumatoid arthritis. This phase of management is but one of its segments and its pursuit alone suffices in relatively few individuals. It must be added to the principles of pain relief and of palliation.

2. *Pain Relief.*—Lowman,[11] in his study of the rehabilitation of patients with severe rheumatoid arthritis, has been impressed with two cardinal features. In contrast to the paraplegic and postparalytic patient undergoing rehabilitation, patients with rheumatoid arthritis have pain, which influences all their activities since rehabilitation procedures may lead to an increase in pain. Pain affects their ability to carry out these procedures and decreases the effectiveness of repetitive training. Lowman also noted that the static characteristics seen in the usual rehabilitation problem are rarely present in rheumatoid arthritis. A patient educated to live with a flexed painful right knee may develop a flexed painful left knee and require further re-education. Pain is ever-present in these individuals with weight-bearing, during use and at rest. Frequently the pain of rheumatoid arthritis is associated with inflammation and the objective evidence thereof, but the latter may be subclinical and our evaluation of a situation then depends completely on the patient's interpretations. These will vary from patient to patient and in a given patient from day to day, depending on factors unknown to us but presumed by some to be associated with changes in barometric pressure, the state of the ego, the conflicts within the household, or the phase of the moon.

Pain brings the patient to the physician and its control must be attempted. Several agents and modalities are available to achieve this result, the choice of which depends upon many factors: the severity of the disease, its duration,

the velocity of its progression, the social state of the patient, his economic status, and such other considerations as the availability of facilities for sanatorium care and the distance between office or clinic and home. The role of each of these forces must be evaluated with respect to their beneficial or deleterious effect. One must remember that one is dealing with a situation in which days or weeks are of little significance and should reckon in months and years. Although pain is of paramount importance to the patient, it is a comforting feature that it is seldom remembered. A pause for assessment of the problem, particularly the speed with which the disease is progressing, is of great value in the long-range picture. In the early stages of rheumatoid arthritis, this is essential to permit a spontaneous remission if it is to occur. In old established disease, long maintained on a sustained plane of activity, this pause will do no harm. There is no urgency in starting treatment except in the mind of the doctor who cannot bear to see his patient suffer. In the early disease, a regimen of salicylates and some slowing down of the pace of life is invaluable to allow the physician to know which way things are going. If economic circumstances permit and the patient's social pattern will not be disrupted, a period of two weeks' observation in a hospital is ideal. During this time, he may be seen frequently, and the philosophy of his disease may be presented to him slowly and not precipitously. Salicylates may be used at doses higher than practicable on an ambulatory basis, a program for living may be worked out, and exercises against resistance may be taught. If such a hospital admission is economically impractical or would disastrously affect the family situation, the same program may be started on an ambulatory basis in a less intense fashion. This latter is more wearing on the patient, requiring more of an expenditure of physical effort. Further, it is more difficult to develop a satisfactory relationship between patient and physician.

If things go well on this program, it should be pursued in a steadfast manner, hoping that a remission will ensue. If the patient and physician are satisfied that a program for a life on a moderately decreased plane of activity can be worked out, "the life of equanimity," much will have been accomplished. Frequently rest splints may be used at night to alleviate pain and to attempt to prevent deformities; the simpler these are, the less expensive and easier made, the better. Gutter splints of plaster or some of the newer heat-moldable plastics are quite adequate. Soft foam rubber arch supports developed from a plaster foot mold poured in heavy petrolatum are often of inestimable value. At this stage, complicated splints and braces are of little use because of the changing pattern of the disease, and too frequently are soon relegated to the attic at no small expense to the patient. One may surmise that this program fosters dependency of the patient on the physician. It does to a certain extent; and excessive dependency is to be deplored.

If things do not seem to be going well, if the intensity of the disease is not partially abated, or if the patient rejects the life of equanimity, several alternative courses may be considered. Each has its hazards, each its shortcomings, as shown in Table III. These various antiphlogistic measures will not be examined in detail since each has been the subject, some of us believe,

of too much discussion. A brief amplification of the table, however, seems indicated. Sanatorium care yields a high remission rate which is often prolonged after the return of the patient to his usual haunts, but this is not always permanent. Untoward effects are those related to prolonged hospitalization. Disuse atrophies, wasting, and osteoporosis can be controlled by careful supervision, but this usually consumes too much time and effort. One must be constantly on guard against fostering too much dependence. The major drawbacks to this type of care are economic ones since suitable facilities are in most instances nonexistent and the cost is exorbitant. If the patient cannot assume the financial burden himself, the cost for adequate care on a routine and not an experimental basis lies beyond the capabilities of most health agencies, either voluntary or governmental.

TABLE III. ADVANTAGES AND DISADVANTAGES OF STANDARD THERAPIES ADVOCATED FOR RHEUMATOID ARTHRITIS

	SANATORIUM CARE	GOLD	HORMONES	BUTAZOLIDIN
1. Remission rate	+3	+2	+4	+1
2. Duration of remission after termination	+3	+2	0	0
3. Speed of onset of remission	+1	+1	+4	+2
4. Hazards	−1	−2	−4	−4
5. Cost	−4	−1	−2	−1

+indicates an advantage.
−indicates a disadvantage.

Gold therapy produces a fairly prolonged remission when successful but has no effect on many patients. It is a simple form of therapy which can be carried out without interfering with the patient's way of life. The onset of the remission is delayed, relapses are the rule within a period of one to two years after cessation of therapy, and the feasibility of maintaining a remission by continuing gold indefinitely has not yet been proved. Toxic reactions ascribed to gold are well known. With the use of BAL (British antilewisite) and/or cortisone, these should no longer be fatal but can assuredly be a major nuisance to the patient, his family, and his physician.

The hormones, ACTH (corticotropin), cortisone, hydrocortisone, and their various analogues, produce a rapid and dramatic remission in most patients with rheumatoid arthritis. They present no great problem in administration but no one has yet answered a simple question: How can a potent antiphlogistic agent, such as cortisone, inhibit the inflammation of rheumatoid arthritis, and still not interfere with normal bodily defenses against the traumatic incidents encountered in daily living? If one adopts the philosophy that growth, maturation, and turnover of tissue are related in their initial phases to the mechanisms

of inflammation,[12] these processes as well will be interrupted during hormone administration. This is all the more pertinent, since to date the antiphlogistic role of these hormones, regardless of the analogue tested, has not been on inflammation alone. When the hormone has had antiphlogistic properties demonstrated, growth and repair have been modified. We need a new type of preparation which will modify inflammation at a different stage in its genesis than is done by these hormones. Another point which makes one somewhat disheartened by the search for newer and more potent analogues is the obvious fact that if inflammation is severe, large amounts of the anti-inflammatory agent are required, inducing the generalized effects on growth, maturation, and turnover mentioned previously. Thus, when inflammation is severe, hormones may be required in amounts so large as to be incompatible with health.

The last difficulties with hormones are those associated with withdrawal and the rebound. When hormones are stopped abruptly or even decreased slowly and the disease remains active, as it does in the great majority of patients with rheumatoid arthritis, a period of intense disease activity may ensue which often may be of greater severity than the original disease. The pattern may be somewhat different with an increase in systemic manifestations and may frequently include visceral involvement.[13] This occurs when the adrenals are fully responsive to corticotropin; therefore replacement-induced adrenal insufficiency is an unlikely basis for their causation. We look upon this phenomenon, perhaps naively, as a release of dammed-up products which the organism has been unable to utilize during the inhibition of inflammation by cortisone. We have not been able to control this type of occurrence and feel that it is a major hazard in hormonal use. An attempt to prevent the systemic hazards of these hormones by the use of a locally effective one, such as by hydrocortisone, has a place in the treatment of rheumatoid arthritis. However, the brevity of action and the necessity of treating many joints frequently in severe rheumatoid arthritis make this seldom a feasible or practical course of therapy.

Phenylbutazone (Butazolidin) achieves a low remission rate in rheumatoid arthritis, is endowed with a major toxic potential, and is rarely used for the long-term type of therapy in this disease. When it does exhibit antiphlogistic properties (it is impossible to predict when this eventuality will occur in peripheral joint rheumatoid arthritis), it is quite helpful. If no toxicity develops, the beneficial effect may be sustained. The percentage of patients reacting favorably after these two qualifications have been met is small and this drug is probably best reserved for gout and Marie-Strümpell spondylitis, if it is to be used at all. It has no real place in the treatment of peripheral rheumatoid arthritis.

As background to each of these forms of therapy, we are convinced that enteric-coated or buffered salicylates should be continued to tolerance on a four times a day schedule (not sporadically only for the relief of pain).

No mention has been made of the true analgesics, the narcotics. The hazards of addiction are so great that we lean over backward to avoid all but codeine, and that only for very short periods in the later stages of disease.

3. *Palliation.*—In the late stages of disease where deformities have developed either through neglect or despite our best efforts, and the patient must

of necessity live at a slower pace, efforts should be directed toward the classic aims of rehabilitation in order to make the patient comfortable in the best situation possible. Pain must still be controlled, and most patients in this category have convinced themselves of the value of the salicylates. Reconstructive surgery done cautiously, a little at a time, has its place in this phase of the disease. Various self-help aids are useful. A listing of these for patients with rheumatoid arthritis has been compiled by Lowman through the Institute of Physical Medicine and Rehabilitation.[14] In these late-disease situations, the ancillary services of the medical profession are needed, such as social service assistance to adapt the patient to his environmental situation. Above all, where irreversible changes are present resulting from chronic disease both in joints and in the patient's response to his environment, it is impossible to effect a complete restoration of the patient to a fully functioning piece of human machinery. If unwisely attempted, it may lead to further deterioration. An example of this is seen in severe disease where large doses of cortisone are needed to obtain relief. Such doses of cortisone can usually be employed only for brief periods because of deleterious side effects, and a necessary withdrawal will destroy the patient's precortisone adjustment to his life situation.

This discussion carries the implication that the sine qua non is the physician spending time with the patient to help him work out problems with his associates by which a life of equanimity may be achieved in his proper milieu. This is basically an admission of ignorance on our part regarding the pathogenesis of rheumatoid arthritis, but the management of the patient cannot wait for the appearance of complete knowledge of the disease. Patience, understanding, and time are required. If sufficient time can be allotted to the patient, his response will often be gratifying. There is no substitute for time. If a short-cut substitute is used, be it cortisone, Butazolidin, or a free sanatorium bed, the results may be disastrous. My plea is for no special medicine, no superknowledge, but only that the physician take the time to know his patient, to work with him toward the solution of his problems, utilizing both common sense and empirically gained knowledge for pain control.

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POSTNECROTIC CIRRHOSIS OF THE LIVER

A Study of Forty-Five Cases

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(Received for publication Oct. 20, 1954.)

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MARCHAND,[1] Mallory,[2] and others have described a type of cirrhosis of the liver, distinct from Laennec's, characterized by necrosis of liver cells, regenerating nodules of hepatic tissue, and the presence of large bands of connective tissue which course irregularly through the liver, all of which stand in contrast, in some areas, to well-preserved normal hepatic architecture. This lesion has been called by a variety of names, among them "subacute or healed acute yellow atrophy," "multiple nodular hyperplasia," "coarse nodular cirrhosis," "toxic nodular cirrhosis," and "postnecrotic cirrhosis or scarring." Until recently, little attempt was made to differentiate postnecrotic cirrhosis clinically from the more common Laennec's variety, although it was recognized that the cirrhosis which followed a severe infectious or toxic hepatitis was usually postnecrotic. In the past few years it has been shown in animal experiments that postnecrotic cirrhosis may be the result of conditions quite distinct from those conducive to Laennec's cirrhosis.

Postnecrotic cirrhosis is an uncommon disease. In order to gain some understanding of its natural history, cases of postnecrotic cirrhosis have been assembled from the experience of hospitals in three cities, and the information thus obtained analyzed so that the symptoms, signs, and course of postnecrotic and Laennec's cirrhosis could be compared.

CASE MATERIAL

Forty-five instances of postnecrotic cirrhosis were selected from the records of The Johns Hopkins Hospital in Baltimore, University Hospitals of Cleveland, and the Research Service, Columbia University Division, Goldwater Memorial Hospital, in New York City. The diagnosis in these 45 patients, all observed between 1936 and 1952, was made on the basis of microscopic examination of tissue obtained in 6 cases by biopsy, in 28 cases at post-mortem examination,

and in 11 cases both by biopsy and at autopsy. The criteria used in establishing the diagnosis were similar to those described by a group of pathologists at the Sixth Conference on Liver Injury of the Josiah Macy, Jr., Foundation,[3] and by Himsworth.[4] They included the presence of broad fibrous bands separating areas of parenchymal hepatic tissue in which the lobular architecture was often relatively well preserved. This was in contradistinction to the characteristic picture of Laennec's cirrhosis, a diffuse fibrosis involving all the lobules, with disruption of the normal relationships within the lobules. Unlike the relatively uniform changes of Laennec's cirrhosis, the lesions in these cases of postnecrotic cirrhosis varied in different parts of the liver, and even from lobule to lobule. Either local or massive areas of necrosis were usually present, as well as evidences of regeneration. Proliferation of the small bile ducts within the fibrosed areas was often profuse. Fatty infiltration of the liver, a common finding in Laennec's cirrhosis, was either absent or minimal. The fibrous bands were often infiltrated with lymphocytes or polymorphonuclear leukocytes. Usually the surface was very irregular, due to the presence of nodules, varying greatly in size, which protruded from the network of fibrous tissue.

Excluded from the series were several cases in which primary carcinoma of the liver was superimposed upon a postnecrotic cirrhosis, and several in which it was not possible to distinguish between Laennec's and postnecrotic cirrhosis. One case of postnecrotic cirrhosis, in a 33-year-old Negro woman with rheumatic heart disease, was not included in this series because the patient had no symptoms which appeared to be referrable to the cirrhosis. Sixteen of the 45 patients had been examined during life by one or the other of the authors. In each case microscopic sections of the liver were reviewed.*

Incidence.—In the present study no data were collected concerning the relative incidence of postnecrotic cirrhosis and Laennec's cirrhosis. At the Boston City Hospital, 8.4 per cent of 550 cases of "well-marked cirrhosis" examined between 1897 and 1931 were diagnosed as "healed acute yellow atrophy" by Mallory.[5] Karsner[6] reported that in his experience about 10 per cent of cases of cirrhosis examined post mortem were postnecrotic. These cases were studied at University Hospitals of Cleveland, but were largely from an earlier period than the cases in the present series. At the Research Service, Columbia Division, Goldwater Memorial Hospital, 15 of 124 patients with cirrhosis were thought to have postnecrotic cirrhosis, but histologic proof of the diagnosis was available in only 7 of these.[7] These 7 cases are among those included in the present study. If the data reviewed are typical, about one-tenth of cases of cirrhosis in the United States may be classified as postnecrotic.

Age.—The ages of 45 patients with postnecrotic cirrhosis at the time that the first symptom was noted are listed in Table I. Two-thirds of the males were 40 years or older, while slightly more than one-half the females were less than 40 at the onset of their disease. No age appeared to be spared. The age distribution did not differ significantly among the three hospitals. Others have

*We are indebted to Dr. Margaret Bevans, Dr. Morgan Berthrong, and Dr. James L. Orbison for their kindness in reviewing the histologic sections.

noted that postnecrotic cirrhosis is relatively more frequent in younger patients than is Laennec's cirrhosis, in which two-thirds of the patients first become ill between the ages of 40 and 59.[8] Thus, 9 of Miller and Rutherford's[9] 10 patients died before their twenty-fifth year, and 24 of the 35 patients described by Kelsall and his associates[10] were less than 40 years of age when they had their first symptom. Patients as old as 80[11] and as young as 2 years[9] have been described, and a possible case in a newly born infant has been reported.[12] Since postnecrotic cirrhosis can apparently follow hepatic injury due to many different causes, this wide age distribution is to be expected.

TABLE I. AGE DISTRIBUTION IN 45 CASES OF POSTNECROTIC CIRRHOSIS

		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	ALL AGES
Males	J. H. Hosp.	1	0	0	0	1	2	0	0	
	Univ. Hosp.	0	0	0	1	0	3	0	0	
	G. M. Hosp.	0	1	2	1	1	3	2	0	
	Subtotal	*1*	*1*	*2*	*2*	*2*	*8*	*2*	*0*	*18*
Females	J. H. Hosp.	1	2	3	1	0	1	2	0	
	Univ. Hosp.	0	0	2	3	4	2	1	1	
	G. M. Hosp.	0	0	2	1	0	0	0	1	
	Subtotal	*1*	*2*	*7*	*5*	*4*	*3*	*3*	*2*	*27*
	Total	**2**	**3**	**9**	**7**	**6**	**11**	**5**	**2**	**45**

Sex.—Laennec's cirrhosis occurs at least twice as frequently in males as in females.[8] In contradistinction, 60 per cent of the patients in the present series were females. The proportion of female patients in the three hospitals studied differed (Table II) for unknown reasons. Despite this disparity in the sex distribution, no distinguishing features could be demonstrated in the clinical course of patients in the three hospitals. Among white patients, 18 were male and 19 female. On the other hand, all of 8 Negro patients were female. It is doubtful whether this finding is significant, since Karsner[6] has reported a number of instances of postnecrotic cirrhosis in Negro males.

TABLE II. SEX DISTRIBUTION IN 45 CASES OF POSTNECROTIC CIRRHOSIS

	MALE	FEMALE
The Johns Hopkins Hospital	4	10
University Hospitals	4	13
Goldwater Memorial Hospital	10	4
Total	18	27

The sex incidence of postnecrotic cirrhosis in various reported series differs considerably. Mallory's[5] group of cases from the Boston City Hospital included 29 males and 17 females. Others[9,10,13,14] have said that the disease is most common in females. Differences in the sex incidence of postnecrotic cirrhosis in different series may represent chance, since all the reported groups are relatively small. On the other hand, the differences may be a reflection of the different etiological mechanisms which may be responsible for the development of postnecrotic cirrhosis, as seen by different observers. In recent years, there has been a great increase in postnecrotic cirrhosis in postmenopausal women in Scandinavia.[15,16] In other cases, postnecrotic cirrhosis has followed injury by toxins to which one sex or another might have greater opportunities to be exposed. Caution must be observed in attempting to attribute an increased susceptibility of either sex to postnecrotic cirrhosis to some obvious causative factor. For example, the greater frequency of Laennec's cirrhosis in males is usually attributed to the greater incidence of chronic alcoholism in their sex. However, among 182 patients with Laennec's cirrhosis who denied alcoholism, 107 were males.[8] It may be that this is only a reflection of the difficulty of obtaining a history of alcoholism in female patients. Nonetheless, there is considerable experimental evidence that male animals are more susceptible than females to various types of hepatic injury.[17-19] In summary, there is no clear-cut evidence that postnecrotic cirrhosis in man is more frequent in one sex than the other.

Kelsall, Stewart, and Witts[10] divided their patients with "chronic hepatitis," most of whom had postnecrotic cirrhosis, into two groups. In those patients in whom the onset of the cirrhosis was insidious, females outnumbered the males three to one. On the other hand, among patients whose cirrhosis appeared to begin as an acute hepatitis which gradually became chronic, the sex incidence was equal. This distinction in the sex incidence of postnecrotic cirrhosis was not the case in the present series.

PATHOGENETIC FACTORS

Race and Nationality.—In New York City, Laennec's cirrhosis is particularly frequent among persons of Italian and Irish extraction.[8] In contrast, postnecrotic cirrhosis did not appear to have a predilection for any ethnic group. Of 45 patients in the present series, only 2 were of Italian and 2 of Irish descent. Other authors have not commented upon any unusual racial predisposition to postnecrotic cirrhosis. An exception to this is the high incidence of postnecrotic cirrhosis in Scandinavia among postmenopausal women, in whom it has appeared as a sequel to severe hepatitis.[15,16]

Family History.—In none of the patients in this series was a family history of cirrhosis of the liver obtained. There are, however, several types of familial postnecrotic cirrhosis. In hepatolenticular degeneration, Wilson's disease, postnecrotic cirrhosis is often present.[21] Such was the case in each of 3 patients with Wilson's disease whom we have studied, although some of the patients described in the literature have been said to have had portal cirrhosis.[22] A

second type of familial postnecrotic cirrhosis occurs in association with the de Toni-Fanconi syndrome. Patients with this disorder have renal glycosuria, hypophosphatemic rickets or osteomalacia, enlargement of the liver and spleen, and aminoaciduria. Himsworth[4] described two patients with this syndrome in whom postnecrotic cirrhosis was found at autopsy, in both cases complicated by carcinomatous changes.

Another possible cause of congenital postnecrotic cirrhosis is transplacental transmission of the virus of acute infectious hepatitis. Bellin and Bailit[12] have reported the unique case of an infant born of a mother with hepatitis. The infant had jaundice and ascites at birth, and cirrhosis, demonstrated by punch biopsy, at the age of 2 months. However, the nature of the cirrhosis in this infant is not clear. Familial postnecrotic cirrhosis may occur because several members of a family are simultaneously affected by acute infectious hepatitis, as recorded by Jones and Minot[23] and later in the case records of the Massachusetts General Hospitals.[24]

Acute Hepatitis.—The extensive hepatic necrosis produced by infectious hepatitis is usually followed by complete healing. In a small number, overwhelming injury is fatal. In another small group, the illness assumes a progressive or intermittent course which results in the production of cirrhosis of the liver. That acute hepatitis might progress to cirrhosis was pointed out in 1923 by Jones and Minot[23] and reaffirmed repeatedly.[25-36] When cirrhosis follows acute infectious hepatitis or homologous serum jaundice, it is usually postnecrotic,[13,28-31,34,37-40] although cases resembling Laennec's cirrhosis have been described.[14,30,32,33,41,42]

The patient's illness began as if it were acute infectious hepatitis in 12 of the 45 cases in the present series. Two of the patients had been exposed recently to others with jaundice; one of these two had also been transfused with blood and plasma five months before symptoms began. A third patient had been under treatment with neoarsphenamine and Mapharsen for six weeks when she became ill with jaundice, nausea, vomiting, and epigastric pain, associated with dark urine and clay-colored stools. In the other 9 instances, no known contact with hepatitis or exposure to hepatotoxic agents was evident.

In addition to this group of 12, there were 6 other patients who gave the history of having experienced an attack of acute hepatitis five to twelve years before the clinical onset of cirrhosis. They were distinguished from the first group only by a latent period between the first episode of jaundice and the subsequent symptoms. In one of these patients, the initial episode of jaundice occurred during therapy with arsphenamine for syphilis. The occurrence of a latent period of many years between the original hepatitis and the subsequent cirrhosis, such as we have observed, has been emphasized by Cullinan[13] and Bloomfield.[25]

There was no significant difference in the frequency of alcoholism among those patients with symptoms suggestive of hepatitis and those who did not give this history.

Postnecrotic cirrhosis has been described as a sequel not only to acute infectious hepatitis but to hepatic injury due to many different substances. Mallory[43] mentioned phosphorus, chloroform, carbon tetrachloride, and bacterial toxins as etiological agents. Perhaps the chemical most frequently implicated in the literature is cinchophen,[44-48] although it is not clear whether this drug is directly injurious to the liver or renders it susceptible to the action of some other agent. Cases of postnecrotic cirrhosis have been reported following exposure to or ingestion of trinitrotoluol,[49,50] dinitrobenzene,[51] synthetic organic hair dyes,[52] trichlorethylene,[10] naphthalene,[53] or inorganic arsenic.[10]

In the present series there were four patients who had been exposed more or less heavily to chemicals which may have hepatotoxic properties. Instances of postnecrotic cirrhosis were observed in a lathe operator who used an unidentified cleaning fluid for three months, and in an alcoholic electrician who used carbon tetrachloride to clean machinery. A third patient had been treated with cinchophen for rheumatoid arthritis, and a fourth had been exposed to benzol and camphor. Benzol is not thought to be hepatotoxic, but acute yellow atrophy of the liver had been observed following the ingestion of camphor.[54]

Four other patients had been treated for syphilis with arsenical compounds. Arsenic is a known hepatotoxic agent, and Mallory[43] attributed some cases of postnecrotic cirrhosis to its effects. In recent years, however, epidemiologic evidence has accumulated that the hepatitis seen in patients undergoing antisyphilitic treatment is in most if not in all cases due to the virus of homologous serum jaundice, transmitted from patient to patient by the use of inadequately sterilized needles and syringes.[34,55,56] It seems reasonable to suppose that postnecrotic cirrhosis in patients treated for syphilis by the injection of an arsenical may be the sequel of homologous serum jaundice acquired in this manner. Whether arsenic modifies the course of this disease is not known.

Thus, it seems likely that postnecrotic cirrhosis may occur in anyone who has an acute hepatitis, but it is not clear why some patients die in the acute stages, others appear to recover completely, and still others develop postnecrotic scarring in the liver.

The severity of the original hepatitis, judged clinically, seems to bear little relation to the later development of cirrhosis. It is possible that constitutional or environmental factors play a role either in rendering the liver more vulnerable or in potentiating the effects of the hepatotoxic agent.

Chronic Alcoholism and Dietary Deficiency.—A relatively high proportion of patients with postnecrotic cirrhosis gave a history of the prolonged consumption of alcoholic beverages in the years preceding their illness. Thirteen (29 per cent) of the 45 patients in this series admitted to chronic alcoholism, including 6 of 18 male patients and 7 of 27 females. Chronic alcoholism was not a factor in any of the cases which appeared before the twentieth year, but in patients older than 20, it occurred with equal frequency among the young and old. Thus a history of alcoholism was obtained in 6 of 16 patients whose first symptoms appeared between the ages of 20 and 39, and 7 of 24 in whom the disease appeared clinically at a later age. As in the case of Laennec's cirrhosis, the nature of the alcoholic beverage did not appear to be important. A number of observers

have commented upon the high incidence of alcoholism in patients with postnecrotic cirrhosis. For example, two of Sheldon and James's[31] three cases were in alcoholics, as were 3 of the 10 cases reported by Stine and Swarts.[57] In other series, alcoholism did not appear to be a factor, but it is not entirely clear whether patients with such a history were not excluded from consideration.[10,13]

Among chronic alcoholic persons, Laennec's cirrhosis is by far the most frequent type of cirrhosis which is encountered. However, in view of recent experimental studies, it is not surprising that in occasional alcoholic persons the lesions observed are those of postnecrotic cirrhosis. The administration of alcohol to experimental animals does not result in hepatic lesions (vide ref. 58, p. 182). However, in patients with cirrhosis of the liver, chronic alcoholism is commonly accompanied by prolonged dietary inadequacy.[59] The possible importance of a deficient dietary intake in the etiology of hepatic lesions has received considerable attention. For example, among patients with cirrhosis studied at the Research Service, Columbia University Division, Goldwater Memorial Hospital, 73 per cent had eaten inadequate diets which were particularly deficient in meat and dairy products.[7]

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Experimental animals fed certain deficient diets develop hepatic necrosis, fatty infiltration of the liver, and cirrhosis. As Daft, Sebrell, and Lillie,[60] Himsworth and Glynn,[61,62] and others[63,64] have shown, whether one finds, on the one hand, fatty infiltration and fibrosis (a complex resembling Laennec's cirrhosis) or, on the other hand, hepatic necrosis depends upon relatively small differences in the composition of the diet. A deficiency of methionine, vitamin E, and a factor present in certain yeasts may result in massive necrosis of the liver.[65,66] If the animal recovers, the lesion which results bears a resemblance to human postnecrotic cirrhosis.[61] When one considers the multiplicity of host and environmental factors in human cases, one would expect the great variations in lesions observed. Indeed, in some patients the hepatic lesions suggest that both postnecrotic and Laennec's cirrhosis are present, but such cases have not been included in the present series.

In the present study, adequate dietary histories were obtained principally in the patients studied in New York City. Of these 14 patients, a history of prolonged dietary inadequacy was obtained in 7, only 3 of whom were alcoholics. One of the nonalcoholic patients had eaten no meat for one year before the appearance of symptoms. The other three nonalcoholic patients had had episodes of acute hepatitis six to fourteen years before the onset of their final illness. These data illustrate the complexity of pathogenetic factors in postnecrotic cirrhosis. In only 5 of the patients in Baltimore and Cleveland, all alcoholics, was a history of an inadequate dietary intake obtained, but the records were inadequate in this respect. One may conclude that it is possible that in some patients an inadequate diet may contribute to the development of postnecrotic cirrhosis.

Other Possible Etiological Factors.—Six of the 45 patients in this series had either serologic evidence or a history of syphilis. There is, however, no evidence that postnecrotic cirrhosis is a syphilitic lesion. Four of the six patients had been treated with one or another arsenical. In two of these, symptoms suggestive

of acute hepatitis occurred during the course of therapy. In one case, these symptoms subsided, but were followed five years later by symptoms which appeared to be referrable to postnecrotic cirrhosis. In the second patient, the symptoms of hepatitis progressed, and the patient died two months later with a typical postnecrotic cirrhosis.

It is difficult to evaluate the various antecedent illnesses described in the patients with postnecrotic cirrhosis. One patient had had a toxic goiter twenty-one years before. It is known that patients with hyperthyroidism often have evidences of hepatic damage clinically and at autopsy,[67] and several cases of postnecrotic cirrhosis in patients with a history of hyperthyroidism have been described.[57] Another patient, a 41-year-old housewife, had had eclampsia fifteen years before. Hepatic damage is a prominent feature of eclampsia, but we are not familiar with any evidence that this lesion will progress to cirrhosis.

The past history of the patients with cirrhosis was otherwise not remarkable. Three of the patients had had chronic constipation for many years, while another had had four to six bowel movements a day for twenty-five years. Chronic ulcerative colitis is occasionally complicated by cirrhosis of the liver. In these patients, the changes observed are often those of postnecrotic cirrhosis rather than Laennec's cirrhosis.[68-75]

Two patients had diabetes mellitus, and two, minor allergies. There were individual patients with Kaposi's sarcoma, rheumatoid arthritis, bronchiectasis, psoriasis, and cor pulmonale, and patients who had histories of typhoid fever, possible rheumatic fever, chronic salpingitis, carcinoma of the cervix, and an unspecified "tumor of womb," but none of these illnesses seemed related to the postnecrotic cirrhosis.

SYMPTOMS OF POSTNECROTIC CIRRHOSIS

The symptoms of the patients with postnecrotic cirrhosis are listed in Table III, and the initial symptoms of this disease in Table IV. Comparison is made with the symptoms of patients in a series of cases of Laennec's cirrhosis.[8] This comparison may not be entirely valid because the two series were assembled over different periods of time, and there may possibly have been a shift in clinical interest.

As has been noted, the initial symptoms and signs in 12 of the 45 cases of postnecrotic cirrhosis resembled those of acute hepatitis, with malaise, anorexia, nausea, vomiting, abdominal distress, icterus, light-colored stools, and dark urine. It is unusual for patients with Laennec's cirrhosis to experience this syndrome at the onset of illness. In other patients, the illness began more insidiously, with such symptoms as weakness, abdominal distress, weight loss, swelling of the abdomen, and edema. In this latter group of patients, the initial symptomatology gave no clue to the type of cirrhosis present.

Abdominal pain was the commonest complaint of patients with postnecrotic cirrhosis, being present in 4 of every 5 cases. In 12 instances, the pain was primarily epigastric but apparently unrelated to the ingestion of food. Nine patients had right upper quadrant pain, sometimes radiating across the abdomen.

Other patients complained of pain elsewhere in the abdomen. In 9 cases, there were episodes of generalized abdominal pain, particularly significant since this was associated with peritonitis in 4 instances. In none of the other patients was the pathogenesis of the abdominal pain evident except in 1 case of gastric ulcer and 1 of portal venous thrombosis.

TABLE III. SYMPTOMS IN 45 PATIENTS WITH POSTNECROTIC CIRRHOSIS: COMPARISON WITH A SERIES OF 386 PATIENTS WITH LAENNEC'S CIRRHOSIS

SYMPTOM	NUMBER OF CASES	PER CENT OF CASES	PER CENT OF CASES OF LAENNEC'S CIRRHOSIS[8]
Abdominal pain and distress	36	80	31
Anorexia	26	58	35
Nausea	21	47	33
Weight loss	18	40	53
Hemorrhagic phenomena	18	40	26
Hematemesis	15	33	27
Vomiting	15	33	30
Weakness at or near onset	14	31	21
Diarrhea	13	29	20
Malaise at or near onset	10	22	3
Pruritus	7	16	3
Oligo- or amenorrhea	7 of 27♀	26	7
Eructation	6	13	7
Constipation	6	13	9
Drowsiness, not preterminal	5	11	*

Also, 4 each: nocturia, neuritic pain, blurred vision
3 each: flatus, heart burn, menorrhagia
2 each: melena without hematemesis, oliguria, fainting spells, polydipsia, gagging, intolerance of fatty foods
1 each: leg cramps, euphoria, yellow tears, sore breasts with menses, hiccough, dyspepsia

*No comparable data.

TABLE IV. INITIAL SYMPTOMS AND SIGNS IN 45 PATIENTS WITH POSTNECROTIC CIRRHOSIS

SYMPTOM	NUMBER OF CASES	PER CENT OF CASES
Onset resembling acute hepatitis*	12	27
Anorexia	11	24
Jaundice	10	22
Malaise	10	22
Weakness	8	18
Epigastric distress	6	13
Weight loss	6	13
Swollen abdomen	5	11
Edema	4	9
Nausea and vomiting	3	7

Also 2 each: grippelike symptoms, light-colored stools, diarrhea, hematemesis, dark urine
Also 1 each: heartburn, wasting of limbs, pruritus, drowsiness, dyspepsia, epistaxes, pain "over spleen," fever, vaginal bleeding, dyspnea

*Individual symptoms are tabulated separately.

The pain in postnecrotic cirrhosis was usually episodic and was occasionally observed in association with bouts of jaundice and fever. Its intensity was described variously, but in eight cases it was definitely severe. Some patients said the pain was sharp, others spoke of it as dull and aching, and still others had griping, colicky, or crampy distress. Despite this prominence of abdominal distress, little attention has been paid to this symptom in the literature, although Yazigi and his associates[11] described right upper quadrant pain in 6 of their 9 cases.

In addition to abdominal pain or distress, most patients with postnecrotic cirrhosis, like those with Laennec's cirrhosis, had a wide variety of symptoms referrable to the gastrointestinal tract. Forty-one of the 45 patients with postnecrotic cirrhosis had one or another abdominal complaint. Excluding those in whom this symptom appeared preterminally, 26 of the patients had anorexia. This usually appeared early in the disease but was often transient. In 11 cases, the anorexia was intermittent, and usually associated with acute episodes of jaundice, malaise, and abdominal distress. Anorexia throughout the course of the disease was the exception rather than the rule. Nausea, with or without vomiting, was common. A few patients complained of heartburn, excessive eructation, or "dyspepsia," and two patients said they were distressed by eating fatty foods. A change in bowel habits was not unusual. Thirteen patients had bouts of diarrhea; in 2, the diarrhea appeared shortly before death. In 1 of these the administration of bile salts was thought to bring relief.

A feeling of *weakness* early during the course of illness was experienced by about one-third of patients with postnecrotic cirrhosis, but severe weakness was noteworthy in only 4 patients. Occasionally, progressive weakness was a prominent feature. *Malaise* early during the disease was recorded in 10 cases, but it is likely that this was actually a more common symptom, since malaise has been a concomitant of most of the frequent bouts of jaundice and abdominal distress in our patients. Kunkel and Labby[30] were impressed with fatigability as a symptom of postnecrotic cirrhosis, and fatigue may be an early complaint.[31,76,77]

A significant *loss of weight* took place in 18, or about one-third of the patients, not including those who lost weight during the terminal months of their illness. In 11, the loss in weight began sometime during the first six months of symptoms. The degree of weight loss varied, but 5 of the patients lost 20 pounds or more.

Hematemesis occurred in one-third of the patients. It was often an early symptom, occurring within the first six months in 6 of the 15 cases. In 2 instances, the sudden unexpected vomiting of blood was the initial symptom of the disease. In 7 cases, the patients died during or just after the first bout of gastrointestinal bleeding. If the patient survived the first hemorrhage, he invariably bled again, and usually repeatedly. In patients with cirrhosis of the liver, hematemesis is usually a manifestation of hypertension of the portal venous bed. Hemorrhage occurs as the result of rupture of one of the thin-walled collateral esophageal varices. *Esophageal varices* were demonstrated at autopsy in 22 of the 39 cases examined, including all but 1 of the 11 patients with hematemesis who were studied post mortem. The varices could be demonstrated by roentgenogram during life in 6 of 10 patients with hematemesis, as well as

in 3 of 11 other patients who did not bleed. In 2 cases, *melena* was present in patients who had not vomited blood. Both of these were found to have esophageal varices at autopsy.

In one patient, a bleeding duodenal ulcer was found at autopsy. This case emphasized the importance of recalling that in the patient with hepatic cirrhosis gastrointestinal hemorrhage may arise at times from a peptic ulcer and not from a varix. Similar cases have been described previously.[11,57,78]

Hemorrhagic phenomena were common. Eighteen patients bled from one or another site. There were 9 with epistaxes, 6 with bleeding gums, 4 with cutaneous purpura, 3 with menorrhagia, and 2 with hematuria. Fourteen of the 18 patients with bleeding phenomena were females. The frequency of bleeding in postnecrotic cirrhosis has been emphasized by Miller and Rutherford,[9] Kelsall, Stewart, and Witts,[10] and Baggenstoss and Stauffer.[14] In patients with cirrhosis, multiple hemostatic defects are common. In the present series, the one-stage prothrombin time was abnormally prolonged in 12 of 15 patients with hemorrhagic manifestations. Prolongation of the one-stage prothrombin time may occur when the concentration of prothrombin, serum prothrombin conversion accelerator, or accelerator globulin is diminished. These substances have all been reported to be deficient in the plasma of patients with hepatic disease.[79,81] Moreover, the one-stage prothrombin time may be prolonged in hypofibrinogenemia, but this defect is exceedingly rare in patients with liver disease.[82,83] The concentration of fibrinogen was normal in the two patients with hemorrhagic symptoms in whom it was measured. Whipple,[79] Harrington and his associates,[80] and Biggs and Macfarlane[84] have observed that the clotting time of a mixture of thrombin and plasma may be prolonged in patients with cirrhosis. This test was not performed in any of the patients in this series. However, in our experience it is almost invariably positive in patients with decompensated cirrhosis. It is possible that this delayed conversion of fibrinogen to fibrin may have contributed to the hemorrhagic diathesis observed. The abnormality described has been ascribed to the presence of a circulating anticoagulant, but preliminary data suggest that in certain cases it may be due instead to a deficiency of a factor in plasma which accelerates the conversion of fibrinogen to fibrin by thrombin.[85] In 3 of 11 patients studied, there were 70,000 platelets per cubic millimeter or less. One of these patients had purpura, but the other 2 had no clinical hemorrhagic phenomena. Bleeding and clotting times were measured in 13 and 14 patients, respectively, and were in all cases normal. Kelsall, Stewart, and Witts,[10] however, have reported that prolongation of the bleeding time, a positive tourniquet test, and moderate thrombocytopenia were not unusual in patients with postnecrotic cirrhosis.

As in Laennec's cirrhosis, evidences of *hormonal abnormalities* were frequent in patients with postnecrotic cirrhosis. Atrophy of the testes was described in only 1 patient, but this sign may have gone undetected in others. Three of the male patients had gynecomastia, while 7 of the females had either oligo- or amenorrhea during their illness. One female patient complained that her voice had become harsh. Several patients have been described in whom catamenia failed to appear at the usual time.[30,76] In one such patient, 18 years of age,

the administration of estrogenic substances was followed by an exacerbation of jaundice and swelling of the abdomen. There is a group of female patients, recently set apart by Bongiovanni and Eisenmenger,[86] in whom severe hormonal changes, reminiscent of Cushing's syndrome, are associated with jaundice, weakness, and, in some advanced cases, cirrhosis of the liver. Whether these patients have postnecrotic cirrhosis is not clear.

Physical Signs.—The signs observed in 45 cases of postnecrotic cirrhosis are listed in Table V. The similarity to the signs of Laennec's cirrhosis is apparent. As might be expected, many of the patients appeared to be chronically ill and poorly nourished at the time that they were first examined in the hospital. However, a surprising number, 16 of the 45, were said to look well nourished or actually obese, and not particularly ill when they were first observed.

TABLE V. PHYSICAL SIGNS IN 45 PATIENTS WITH POSTNECROTIC CIRRHOSIS: COMPARISON WITH A SERIES OF 386 PATIENTS WITH LAENNEC'S CIRRHOSIS

PHYSICAL SIGNS	NUMBER OF CASES	PER CENT OF CASES	PER CENT OF CASES OF LAENNEC'S CIRRHOSIS[8]
Ascites	41	92	78
Jaundice	40	89	65
Palpable liver	34	76	75
Edema	32*	71	61
Palpable spleen	19	42	44
Fever without apparent cause	18	40	24
Hemorrhoids	15	33	27
Dilated veins	14	31	24
Hydrothorax	12	27	6
Liver breath	11	24	†
Vascular spiders	10	22	†
Acneform rash	9	20	†
Palmar erythema	7	16	†
Pigmentation over shins	4	9	6

Also, 3 each: Red tongue or glossitis, prominent eyes, clubbing of fingers
2 each: Bradycardia, smooth tongue, injected conjunctivae, pharyngeal erythema, irregular pulse
1 each: Fundal hemorrhage, spongy gums, atrophic margin of tongue, ataxia, pretibial ulcer, spoon-shaped nails, cyanosis, petechiae

*Including 2 patients without ascites, 4 patients before ascites was noted, and 2 patients with nephritis.

†No comparable data.

The most striking physical finding in postnecrotic cirrhosis was *jaundice*, which was present during the course of 40 of the 45 patients in this series. In contrast to Laennec's cirrhosis, icterus in postnecrotic cirrhosis was often an early symptom. It was noted within a few weeks of the onset of symptoms in 16 patients, and within the first six months in 12 more. The early appearance of icterus was observed with equal frequency in alcoholic and nonalcoholic patients. Nine patients thought that the degree of icterus was fairly constant throughout

their illness, but clinical and laboratory studies suggested that it was either fluctuating in intensity or actually intermittent. A transient increase in the degree of icterus was often associated with a return of such symptoms and signs as anorexia, nausea, vomiting, dark urine, and light-colored stools, suggesting an exacerbation of acute hepatitis.

Seven of the patients complained of *pruritus*, a symptom which may actually have been present but unrecorded in other cases. One of these 7 patients itched even though no icterus was present.

In many patients, the icterus was of considerable severity, as judged by the concentration of bilirubin in the serum. This test was performed in 31 patients. In 1, the maximum value recorded was less than 1.0 mg. per 100 ml. of serum. In 16, the bilirubin was between 1.1 and 5.0 mg. per 100 ml.; in 11, it was between 5.1 and 20.0 mg. per 100 ml.; and in 5, it was greater than 20.0 mg. per 100 ml. In 11 patients, the icterus index was measured instead of the serum bilirubin. In 2 of these, the maximum icterus index was 10 or less; in 5, it was between 11 and 20; and in 4, it was 50 or more.

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At least 21 of the patients thought that their icterus was associated with the presence of dark urine, and 22, with light or clay-colored stools. As in the case of icterus, these signs usually appeared early during the patients' illness, and were usually fluctuating in intensity or present only intermittently. The urine was tested for bilirubin in 33 patients, and this pigment was present in 28 and absent in 5 cases. In 25 patients the urine was also examined for urobilinogen. This chromagen was excreted in abnormally large amounts in 22 of the patients; its excretion was normal or equivocally increased in 3. In 2 additional patients, the urinary urobilin was elevated. The stool was examined for the presence of stercobilin-like pigments in 24 patients. In 7 of these, no pigment was detectable on one or more occasions, but quantitative studies were not made. In Lichtman's experience,[87] clay-colored stools are common in postnecrotic cirrhosis.

The prominence of icterus in many patients with postnecrotic cirrhosis, emphasized by most observers, may make it difficult to differentiate this disease from primary biliary cirrhosis. Certain laboratory tests were of some value in this differentiation. In primary biliary cirrhosis, the serum alkaline phosphatase activity is usually greatly increased.[89,90] In 22 patients with postnecrotic cirrhosis, the alkaline phosphatase was determined by Bodansky's method. In 3, the highest value recorded was less than 4 units. In 7 others, the phosphatase activity ranged from 5 to 10 Bodansky units, values uncommon in patients with obstructive jaundice. In 9 cases, activities from 10 to 19 units were found, values which were elevated, but to a lesser degree than usually seen in primary biliary cirrhosis. In 3 cases, however, the alkaline phosphatase was as high as 22 to 28 units. Similarly, in 7 other patients, the alkaline phosphatase activity, measured by Shinowara's method, was normal in 2 cases, slightly elevated in 3, and increased to 15 to 30 units in 2 others. In one patient, the alkaline phosphatase activity, measured by the King-Armstrong technique, varied from 18 to 25 units, moderately elevated values. In most patients, then, the

alkaline phosphatase activity was either normal or elevated to a lesser degree than in the usual patient with primary biliary cirrhosis.

A second laboratory test valuable in the differentiation between postnecrotic and primary biliary cirrhosis is the determination of the concentration of cholesterol in serum. In primary biliary cirrhosis, the serum cholesterol is usually elevated, sometimes to a remarkable degree.[90] The serum cholesterol was measured in 39 patients with postnecrotic cirrhosis. In 16 the minimal recorded concentration of total cholesterol was between 65 and 119 mg. per 100 ml. In 17 others it ranged from 120 to 199. In 6, the cholesterol concentration was above 200 mg. per 100 ml. In at least 3 patients the cholesterol concentration was initially above 300 mg. per 100 ml. and then fell to lower levels as the disease progressed. It was 300 mg. per 100 ml. or higher in 2 other cases. Cholesterol esters were measured in only 10 patients. Although the esterified cholesterol was never less than 40 per cent of the total, the absolute concentration of esters was less than 50 mg. per 100 ml. in 4 patients. Thus, both hypocholesterolemia and hypercholesterolemia were observed in patients with postnecrotic cirrhosis, and where serial data were available, the cholesterol usually fell during the course of the disease. In those patients who did have hypercholesterolemia, the presence of a normal or only slightly elevated alkaline phosphatase activity helped to rule out the diagnosis of primary biliary cirrhosis.

Swelling of the abdomen, attributable to ascites, occurred at some time during the course of 41 patients, approximately 90 per cent of the present series. Ascites was observed in all the male patients, and all but 4 of the females. In 13 cases, it appeared within two months of the onset of symptoms, and in the rest, from four months to eight years later. Among the 13 patients whose ascites appeared within the first two months, 7 were alcoholics, while among the 28 whose ascites appeared later, only 5 were alcoholics.

Once ascites appeared, it tended to remain constant or progress, but there were 8 patients in whom there was a remission from ascites. In 1 of these patients, transient ascites was observed after a hematemesis, and in another, postoperatively. The ascitic fluid was examined in 21 patients. Unless peritonitis was present, it usually had the characteristics of a transudate. In 20 cases, the highest specific gravity recorded was 1.015 or less, and in the other case, 1.017. The protein content of the ascitic fluid varied widely. In 8 patients it was less than 1.0 Gm. per 100 ml., in 7 between 1.0 and 1.9 Gm., in 2 between 2.0 and 2.9 Gm., and in 2 others more than 3.0 Gm. per 100 ml. Experimental studies on ascites indicate that the protein content of ascitic fluid bears a direct relationship to the concentration of the plasma proteins.[91] None of the fluids was bloody, and the highest red blood cell count recorded was 700 per cubic millimeter. In 18 of 20 fluids the white blood cell count was less than 1,000 per cubic millimeter. In two others, there were 2,500 and 10,000 leukocytes per cubic millimeter, respectively, but in both instances peritonitis was present. In 1 patient, the ascitic fluid looked chylous; in this case, the specific gravity was 1.009 and the fluid contained 1 per cent protein, and between 68 and 112 cells per cubic millimeter.

Twelve of the 45 patients had *hydrothorax*, always in association with ascites, a finding emphasized by Kelsall and his associates.[10] This was demonstrable by roentgenogram in 5 patients, and at autopsy in the others. There was no predilection for one pleural cavity or the other, and it was often bilateral. Despite the elevation of the diaphragms as the result of ascites, and despite the hydrothorax, severe *dyspnea* was present in only 8 patients. Two of these had myocardial and pulmonary disease. *Clubbed fingers*, which are not unusual in Laennec's or primary biliary cirrhosis, were present in 3 patients.

Peripheral edema was common in patients with postnecrotic cirrhosis and was observed in 32 patients. In most, the edema was dependent, but 2 had transient facial edema, as had been observed by Pratt and Stengel.[26] All of the patients with edema had ascites at some time, but it is noteworthy that in 6 patients at least six months elapsed between the appearance of edema and the detection of ascites. The edema was usually mild, but in several patients severe swelling was noted, particularly during the last weeks before death.

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Bouts of *fever* were frequent in postnecrotic cirrhosis, elevations in temperature being recorded in at least 33 patients. In 15 instances, an extrahepatic cause of the fever was present, such as infection or gastrointestinal hemorrhage. However, there were 18 patients in whom an elevation of temperature occurred in the absence of any obvious cause. This fever was usually of slight degree and irregular in character. In 6 of the 18 patients, fever was observed during episodes of icterus and was part of the hepatitis-like picture which has been described. In 4, the fever was noted only during the last weeks of the patient's illness. In others, irregular fever seemed unrelated to any particular incident in the course of the disease. Similar low-grade fever is commonly observed in patients with Laennec's cirrhosis.

Sixteen of the 45 patients were said to have *vascular spiders*, and 7, *palmar erythema*. It is likely that the latter sign, a blotchy reddening of the thenar and hypothenar eminences sometimes extending up the volar surfaces of the fingers and the dorsum of the distal phalanges, was actually present more frequently, since in our experience it is often overlooked. Nine of the patients had acneform eruptions; there was no sexual predilection for this sign. In 4 patients, 2 of whom were chronic alcoholics, brownish pigmentation of the shins was described. Kelsall, Stewart, and Witts[10] believed that in patients with subacute and chronic hepatitis generalized muddy brown pigmentation was relatively frequent; in 2 cases, biopsy demonstrated melanin in the skin.

The *liver* was palpable at some time during the course of postnecrotic cirrhosis in 34 of 45 cases. The degree of enlargement was usually moderate; in only 4 cases was the liver said to be more than one handbreadth below the costal margin. In 4 instances, the liver was tender, but other patients did not complain of this. The liver seemed to shrink during the course of the illness of 13 of the 34 patients with palpable livers. Shrinkage of the liver has been described by Yazigi[11] and by Kunkel and Labby.[30] At autopsy, the liver was usually either normal or diminished in size. The average weight of the liver in 35 adult cases was 1,280 grams, about 400 grams less than the average in 108 cases of Laennec's

cirrhosis.[8] There was very little correlation between the last recorded observation on the palpability of the liver and its weight post mortem, although the average weight of 19 palpable livers was 1,500 grams and of 16 nonpalpable livers, 1,030 grams. The same discrepancy between the palpability of the liver and its weight was noted previously in Laennec's cirrhosis[8] and was earlier emphasized by Jones.[92] Rarely, the liver may be very large; in one case cited by Mallory,[2] it weighed more than 3,500 grams.

The *spleen* was palpable at some time during the course in only 19 of the 45 patients with postnecrotic cirrhosis. Its weight was measured in 30 cases, and averaged 540 grams, not appreciably different from the average weight of the spleen in Laennec's cirrhosis[8] (although Himsworth[4] wrote that the splenic enlargement is greater in postnecrotic than in diffuse cirrhosis). The palpable spleens weighed more than those which were not palpable, averaging 825 and 324 grams, respectively. It is of interest that 26 of the 30 spleens weighed more than 200 grams. Spleens which were greatly enlarged were often not felt, usually because the presence of ascites made examination of the abdomen difficult.

Dilated veins on the abdominal and lateral thoracic walls were observed in 15 of the 45 patients. These veins are presumably collateral channels through which the portal blood flow is diverted to the systemic circulation, and as such they are direct evidence of impedance of the portal blood flow. Nonetheless, there was no correlation between the presence of these veins and the occurrence of bleeding into the gastrointestinal tract, an event usually due to the rupture of gastric or esophageal varices. *Hemorrhoids* were observed in 15 patients, 2 of whom thought that these veins appeared about one year after the onset of other symptoms of cirrhosis. However, it is unlikely that hemorrhoids were more frequent than in the population at large. None of the patients had a caput medusae, although this very rare collection of paraumbilical veins has been described in postnecrotic cirrhosis.[10 87]

Frank *peripheral neuritis* was present in 2 alcoholic male patients, and 2 other patients, 1 an alcoholic, had "neuritic" pains in the legs. *Drowsiness* was observed in 2 patients early during their illness. Three had repeated *fainting spells* or episodes of faintness. A wide variety of *mental reactions* was observed, including hysteria, negativism, euphoria, deterioration of personality and judgment, disorientation, perseveration, and excitement.

Twenty-seven patients died after a period of so-called *cholemia*, which differed in no way from that seen in patients with hepatic failure due to other causes. Typically, the patients were progressively drowsy, stuporous, and finally comatose. The breath acquired the typical hepatic fetor. The patients in cholemia at times had convulsive twitching of the extremities and nuchal and facial muscles. Two had carpopedal spasm. There might be cogwheel rigidity of the extremities and hyperextension of the arms and legs. The neck was sometimes stiff. At times, the deep tendon reflexes were exaggerated, and ankle clonus could be elicited. The Babinski reflex usually became positive. One patient had a generalized convulsion during this period. Despite all these symptoms and signs, the cerebrospinal fluid was unremarkable in the few cases in which

it was examined, and in only one case were significant neurological lesions observed post mortem, namely, cystic degeneration of the lenticular nuclei in a 52-year-old alcoholic man in whom there was no clinical reason to suspect Wilson's disease. In addition to the 27 patients who died in cholemia, there was 1 patient who had a remission after a period of cholemia. Transient recovery from cholemia was noted in 2 ultimately fatal cases.

INTERCURRENT ILLNESSES

Infections of various types were by far the most frequent complications of postnecrotic cirrhosis. Eight patients had peritonitis, each with fatal consequences. In 1, the peritonitis appeared to be the extension of a retroperitoneal abscess. In others, it was possible that the peritonitis was the result of infection through a paracentesis wound. Eight patients had *pneumonia*, usually as a terminal event, although 1 patient survived this complication. Isolated instances of acute ulcerative laryngitis, chronic laryngotracheobronchitis, peritonsillar abscess, streptococcal sore throat, multiple skin abscess, streptococcal cellulitis of the face, and chronic ulcerative cystitis were also observed. Terminally, several patients had *bacteremia* due to *Escherichia coli* in 2 cases, *Staphylococcus aureus* in 2 others, and *Streptococcus viridans* in another. Three of these patients also had peritonitis.

Three patients were found to have chronic, and a fourth, acute interstitial *pancreatitis*. Other lesions of the gastrointestinal tract were occasionally observed. Two patients had *peptic ulcers*, a lesion seen with considerable frequency in patients with Laennec's cirrhosis,[93,94] and also reported repeatedly in association with postnecrotic cirrhosis.[11,26,31] *Phlegmonous enteritis* was found at autopsy in 5 cases. It is likely that this complication was actually more frequent, since these 5 cases were all patients at Goldwater Memorial Hospital, where there has been a special interest in this lesion. Phlegmonous enteritis has also been described in cases reported previously.[9,31,95] One patient had *parotitis* preterminally.

At autopsy, portal and splenic *venous thromboses* were found in 2 patients, and splenic thromboses alone, in a third. A fourth developed a thrombosis at the site of a renal-splenic vein anastamosis and died after repeated hematemeses.

Chronic *renal lesions* were frequent among the patients studied. Three had chronic glomerular nephritis, demonstrable at autopsy. Four others had chronic pyelonephritis, complicated in one instance by the presence of renal calculi. One patient had active renal tuberculosis, and another, congenital polycystic kidneys. The frequency of renal lesions in cirrhosis of the liver has been commented upon before.[96,97] At least 3 patients, who died in cholemia, had tubular lesions suggestive of nephrosis. It is of interest in this regard that experimental hepatic injury, whether induced by toxins or diet, is almost invariably accompanied by renal lesions.

Twenty-eight patients had proteinuria, ranging from slight traces to "three plus," but many had negative tests on other occasions. In a few patients, there was two to three plus proteinuria preterminally. Those who had more than

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one plus proteinuria earlier during their illness had one or another of the renal lesions described. Pyuria, present at one time or another in 8 patients, was usually associated with chronic nephritis or acute or chronic urinary tract infections. Significant hematuria was present in 5 patients, 3 of whom had nephritis, 1 cystitis, and 1 a generalized hemorrhagic diathesis. Only 7 patients had cylindruria, in 3 cases with nephritis, once with renal calculi, and in 3 associated with terminal cholemia.

Renal function tests were performed in a limited number of patients. The excretion of phenolsulfonphthalein, measured in 12 patients, was never significantly impaired, nor was the urea clearance, tested in 10. The serum nonprotein nitrogen was determined in 33 cases. Elevated NPN levels were associated with hematemesis or cholemia. In 22 patients, the highest value recorded was 40 mg. per 100 ml. or less. In 2 patients, the concentration of NPN was 52 and 58 mg. per 100 ml., respectively, after a hematemesis. In 7 others, the NPN was between 50 and 98 mg. per 100 ml. preterminally; 2 of these patients had chronic glomerulonephritis, 1 had peritonitis, and all 7 were in a state of cholemia. Similarly, the concentration of urea nitrogen was measured in 25 cases, and was normal except in 1 patient with nephritis, 1 with chronic pyelonephritis, 1 of 4 patients who had had recent hematemeses, and in 5 cases, during preterminal cholemia.

MISCELLANEOUS LABORATORY DATA

Blood Counts.—In periods remote from hemorrhage, 23 of 45 patients had red blood cell counts of less than 4,000,000 per cubic millimeter, but all but one count was greater than 3,000,000. The concentration of hemoglobin in 22 of 45 cases was between 9 and 12 Gm. per 100 ml., and the hematocrit was between 29 and 37 per cent in 10 instances. In 11 cases, the mean corpuscular volume of the red cells was between 100 and 113, but greater macrocytosis than this was not recorded. The mean corpuscular hemoglobin concentration in the 26 cases in which it could be calculated was normal, between 30 and 38, in all but one case, in which it was 28. Reticulocytosis of 3 to 11 per cent was recorded in 3 of 6 counts performed at times when the patients were thought not to be bleeding. The frequent occurrence of hemolytic anemia in patients with hepatic disease has been emphasized by Watson.[98] In the present series, the fragility of the red blood cells to hypotonic solutions of sodium chloride was normal in the 4 cases tested, and sickle-cell preparations were negative in 3 others. The question may be raised whether a part of the increased excretion of urinary urobilinogen, seen in patients with chronic hepatic disease, may not be secondary to a hemolytic process.

The white blood cell count was less than 3,000 per cubic millimeter in 5 cases, between 3,000 and 5,000 in 17 cases, and between 5,000 and 10,000 in 16 cases. In 5 others the leukocyte count was between 11,000 and 15,000 in the absence of obvious infection or hemorrhage. These complications were accompanied by a leukocytosis. Elevation of the white blood cell count was also seen in 3 patients preterminally, without obvious cause. The differential count was unremarkable except that 4 patients had eosinophilia of 7 to 14 per cent, and

two had basophilia of 3 and 4 per cent, respectively, although at other times, normal values were recorded.

The *sedimentation rate*, determined by Wintrobe's method, was measured in 32 patients. Uncorrected for the hematocrit, it was less than 20 mm. in one hour in 10 patients, and 20 mm. or more in the other 22.

A number of tests of liver function were performed in addition to those mentioned previously. *Serum albumin* and *globulin* determinations, measured by Howe's technique, were made in 41 patients. In 33, the minimal concentration of serum albumin was less than 3.0 Gm. per 100 ml. In 5, it was between 3.0 and 3.9 Gm. per 100 ml., and in only 3 was it 4.0 Gm. or more. The serum globulin was less than 3.0 Gm. in only 6 patients, was between 3.1 and 4.0 Gm. in 14 patients, and was elevated to 4.1 Gm. per 100 ml. or more in 20 patients, 4 of whom had concentrations of serum globulin of 6.3 Gm. per 100 ml. or higher. In 1 patient, the serum globulin was 10.2 Gm. per 100 ml., and electrophoretically, about 50 per cent of the total serum proteins was gamma globulin. A normal serum protein concentration had been determined in this patient five years before the onset of symptoms. The very high serum globulin seen in occasional patients with postnecrotic cirrhosis had been noted a number of times before,[28,99-101] and Zimmerman, Heller, and Hill[101] have also observed that the elevation is due primarily to an increase in the gamma globulin fraction. Hyperglobulinemia of this magnitude is not ordinarily seen in either Laennec's cirrhosis or primary biliary cirrhosis, and its presence is therefore of diagnostic value. Bongiovanni and Eisenmenger[86] observed exteme hyperglobulinemia in a group of female patients with chronic hepatic disease of unknown etiology associated with clinical features of hyperadrenalism. None of the patients in the present study had a similar syndrome.

The *cephalin-cholesterol flocculation test* was performed in 29 patients and was positive, 3 plus or 4 plus, in 28 of these. Similarly, the *thymol turbidity test*, performed in 12 patients, was abnormal in ten. The great frequency of positive cephalin flocculation and thymol turbidity tests was emphasized by Kunkel and Labby.[30]

Bromsulphalein excretion tests were performed in 28 cases. Thirty minutes after an injection of 5 mg. of the dye per kilogram of body weight, more than 10 per cent was retained in the serum in 25 patients. However, in 10 of these, the serum bilirubin concentration was 2.0 mg. per 100 ml. or higher. As Mills and Dragstedt[102] pointed out in 1936, the BSP is unreliable in the presence of jaundice because the serum bilirubin interferes in some manner with the excretion of the dye.

The gall bladder was examined roentgenographically in 13 patients. In 4, it filled with dye normally, but in the other 9, it could not be seen. Presumably, the liver failed to excrete the dye rapidly enough to permit satisfactory x-ray studies.

PROGNOSIS

It is difficult to determine the prognosis in postnecrotic cirrhosis from the data in the present series, since the cases were selected because adequate histologic studies could be made. As a result, with one exception, only fatal cases

have been included, and data concerning prognosis are thus biased. Moreover, postnecrotic cirrhosis is occasionally found at autopsy in patients who have no symptoms during life suggestive of hepatic disease, and it is therefore likely that in some cases it is not a fatal lesion. Among the 45 patients in the present series, 29 (64 per cent) survived for at least one year after the onset of symptoms, and 10 (22 per cent) were still alive at the end of five years. Every patient was known to be dead by the eleventh year after the onset of symptoms except for one child, a girl who was still living after 7 years: in this case, the diagnosis was made on the basis of a typical biopsy specimen obtained at operation. In contrast, in more than 60 per cent of fatal cases of Laennec's cirrhosis observed between 1916 and 1938 the patient died within one year of the first symptom.[8] Thus, the immediate prognosis of postnecrotic cirrhosis may be somewhat better than that of Laennec's cirrhosis.

The appearance of ascites was a grave event in the course of postnecrotic cirrhosis. Of 41 patients with this sign, 22 per cent died within one month, 56 per cent within six months, and 68 per cent within one year of its appearance; all had died within six years. These data are of the same order of magnitude as those on patients with Laennec's cirrhosis and ascites,[8] treated during the years 1916 to 1938. In contrast, only 35 per cent of patients with Laennec's cirrhosis treated with a highly nutritious regimen died within one year after the onset of ascites.[7]

On the other hand, icterus was less ominous in postnecrotic cirrhosis than in Laennec's cirrhosis. Sixty per cent of patients in the present series survived six months, 53 per cent one year, and 18 per cent five years after the appearance of jaundice. This calculation excludes those episodes of icterus which preceded the apparent onset of cirrhosis. Jaundice thus was an earlier symptom than in Laennec's cirrhosis, in which 74 per cent of a group of patients treated between 1916 and 1938 died within twelve months of its appearance.[8]

The patients with postnecrotic cirrhosis did not stand the effects of hematemesis well. Of 17 patients who had gastrointestinal hemorrhage, 7 died within one month of the first episode, and 13 expired within one year. Similar periods of survival were noted in Laennec's cirrhosis.[8]

The literature as well as our personal experience suggests that this disease runs its course more or less indifferent to therapeutic measures. A program similar to that employed for Laennec's cirrhosis usually is prescribed, but with less hope for therapeutic success. Bed rest, nutritious diet, avoidance of fatigue, and protection against infections are the chief measures available. Recently we have used cortisone in the treatment of acute exacerbations characterized by fever, jaundice, and abdominal distress. This limited experience suggests that cortisone may be valuable, and cautious trial with this agent at such times is worthy of consideration.

CAUSE OF DEATH

Forty-four of the 45 patients in this series died, and in all but one instance, information was available concerning the cause of death. In 27 cases, death occurred after a variable period of *cholemia*. In 16 of the 27 cases, however,

cholemia was associated with or secondary to some other condition which may have precipitated hepatic failure, such as hematemesis, renal failure, infection, or an operative procedure. In all, 13 patients died following *gastrointestinal hemorrhage*. Seven had terminal *peritonitis*, in one case associated with retroperitoneal abscess, and in another, with *E. coli* bacteremia. Five patients had *pneumonia* preterminally, one after an operation and the others in association with cholemia. Four patients died postoperatively, in 3 instances in association with cholemic symptoms, and in the fourth, with bronchopneumonia and acute parotitis. Finally, 2 patients died in cardiac failure and 3 in renal failure. In the latter 3, the symptoms of renal failure and of cholemia appeared to merge. Cases have been described in which the patient bled to death from the gums and nose,[30] died because of the incarceration of a femoral hernia,[57] or had pulmonary infarction.[58] In general, then, most patients with postnecrotic cirrhosis died of cholemia, hematemesis, infection, or as the sequel to a surgical operation.

POSTNECROTIC CIRRHOSIS AND CARCINOMA

Those cases in which postnecrotic cirrhosis was complicated by neoplasm were excluded from the present series, and it was not possible to determine the concurrence of the two diseases. There is evidence that carcinoma of the liver is associated with postnecrotic cirrhosis relatively more frequently than with Laennec's cirrhosis. For example, Mallory[2] observed 3 cases of primary carcinoma among 46 cases of healed acute yellow atrophy, and only 3 among 270 cases of alcoholic cirrhosis. Lynch[103] thought that all 8 cases of primary carcinoma of the liver were secondary to healed acute yellow atrophy, and recently Sepulveda, Rivera, and Rojas[104] reported that in Mexico City, primary carcinoma was most frequent in patients with postnecrotic cirrhosis. Other cases have been reported by Sheldon and James[31] and in the case records of the Massachusetts General Hospital.[105] One wonders whether primary carcinoma of the liver may not arise in these cases from the regenerating liver tissue which is so characteristic of the postnecrotic lesion.

SUMMARY AND CONCLUSIONS

The natural history in 45 proved cases of postnecrotic cirrhosis of the liver has been reviewed and compared with that of Laennec's cirrhosis. This type of chronic liver disease is characterized by necrosis of liver cells, regenerating nodules of hepatic tissue, the presence of large bands of connective tissue coursing irregularly through the liver, and, in some areas, preservation of the normal hepatic architecture.

Laennec's cirrhosis occurs at least twice as frequently in males as in females. In contrast, 60 per cent of our 45 patients with postnecrotic cirrhosis were female. The disease appears at any age, and is relatively more frequent in younger patients than is Laennec's cirrhosis. Since postnecrotic cirrhosis may follow hepatic injury due to several seemingly unrelated causes, the wide age distribution and relatively equal sex incidence are not surprising.

The most common pathogenetic factor in the present series appeared to be acute hepatitis. The parenchymal injury in acute hepatitis is usually followed by complete healing. In a few cases, the disorder is fatal. In another small group, the illness assumes a progressive or intermittent course in which cirrhosis may appear. In most instances, this cirrhosis is of the postnecrotic variety. In 12 cases in the present series, the patient's illness began as if it were an acute hepatitis, which then failed to heal. Six other patients had a history of an attack of acute hepatitis five to twelve years before the clinical onset of cirrhosis and were distinguished from this first group only by the latent period between the first episode of jaundice and subsequent symptoms. It must be emphasized that no proof was obtained that any of these 18 cases was the result of infection with the virus of infectious hepatitis.

Postnecrotic cirrhosis has also been reported to result from hepatic damage due to a number of chemical agents, including trinitrotoluol, arsenic, phosphorus, chloroform, carbon tetrachloride, trichlorethylene, camphor, dinitrobenzene, naphthalene, and cinchophen. In the present series 4 patients had been exposed to hepatotoxic agents, and another 4 had been treated for syphilis with parenteral injections of arsenical compounds. Twenty-nine per cent of the patients in the present series admitted the prolonged consumption of alcoholic beverages in the years preceding their illness. Whether postnecrotic cirrhosis in these alcoholic patients was related to concomitant nutritional deficiency or whether they were more susceptible to other hepatotoxic chemical or infectious agents was not possible to determine. It is noteworthy that in 12 of the 45 patients it was impossible to discover any possible pathogenetic or etiological agent.

At the onset the symptoms of postnecrotic cirrhosis in 12 of the 45 patients were similar to those of acute hepatitis. This is decidedly different from Laennec's cirrhosis, in which such a dramatic onset is unusual. In the other 33 patients, the disease appeared insidiously and the initial symptomatology did not suggest the type of cirrhosis present. Abdominal pain or distress was present in a great majority of the patients, and symptoms referrable to the gastrointestinal tract seemed more prominent than in Laennec's cirrhosis. Hematemesis occurred in one-third of the patients; if the patient survived the first hemorrhage he invariably bled again. Bleeding tendencies in the form of epistaxis, gingival bleeding, and purpura were frequent.

The physical signs of postnecrotic cirrhosis were similar to those of Laennec's cirrhosis. However, malnutrition was often much less conspicuous; one-third of the patients were described as well nourished. Jaundice was an early and often persistent sign. In many patients, transient increases in the intensity of the jaundice were associated with the return of symptoms suggestive of acute hepatitis. In the jaundiced patient, the lower serum cholesterol and serum alkaline phosphatase activity helped to distinguish postnecrotic from primary biliary cirrhosis. Ascites was a common sign which appeared earlier during the clinical course in alcoholic than in nonalcoholic patients. Other frequent signs were fever, hydrothorax, peripheral edema, and enlargement of the liver and spleen; at autopsy the weight of the liver averaged less than in Laennec's cirrhosis.

Of interest was the great frequency of positive cephalin cholesterol flocculation and thymol turbidity tests. A few patients had extreme hyperglobulinemia, a useful diagnostic aid.

Postnecrotic cirrhosis is occasionally found at autopsy in patients whose clinical course gives no hint of the possibility of liver disease. For this reason, it seems likely that it may sometimes be compatible with an otherwise normal life. Once symptoms have appeared, however, the prognosis is poor. In this particular series, one-third of the patients died within one year of the first symptom, and only one-quarter survived five years. The most frequent causes of death do not differ from those of other types of cirrhosis—cholemia, gastrointestinal hemorrhage, and infection. Although the disease appears to wax and wane, it is almost invariably fatal, and present therapy seems to be without effect. Occasionally, carcinoma of the liver complicates postnecrotic cirrhosis. Conversely, a number of reports have emphasized that the cirrhosis observed in patients with carcinoma of the liver is more frequently postnecrotic than one would expect.

There are many gaps in our knowledge about this disease. (a) It is still uncertain whether it can be the result of viral hepatitis, although this appears to be the case in a sizable number of patients. If it is, then some additional factor would seem to be involved, since almost all patients with viral hepatitis recover. Whether host or environmental factors or both determine the outcome is not known, although the occurrence of postnecrotic cirrhosis does not seem to be related to the severity of the initial hepatitis. (b) Its pathogenesis is not understood. Does it develop very quickly, as seems to be the case under some experimental conditions, and then remain latent for a period of time until symptoms appear, or do the anatomic changes develop slowly over a period of years? (c) It is not clear whether human postnecrotic cirrhosis can be caused by nutritional deficiencies, as is the case in experimental animals, or whether nutritional deficiencies will potentiate a lesion resulting from infectious or toxic damage. Finally, an effective therapeutic program for patients with postnecrotic cirrhosis is yet to be devised.

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IDIOPATHIC CARDIOMEGALY

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(Received for publication Dec. 15, 1954.)

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IT IS easier to write upon a disease than upon a remedy. The former is in the hands of nature, and a faithful observer, with an eye of tolerable judgment, cannot fail to delineate a likeness. The latter will ever be subject to the whims, the inaccuracies, and the blunders of mankind." Thus, in 1778, wrote William Withering[1] to his "very valuable friend, Dr. Stokes of Stourbridge" concerning "the Digitalis." It is the easier course that I have chosen.

Cardiac hypertrophy of obscure origin is the dominant feature of a group of cases presenting distinctive clinical and pathologic features. The syndrome is observed most frequently, but not exclusively, in young adults. The earliest examples which have come to our attention were reported from France: the first by Josserand and Gallavardin[2] in 1901, the second by Laubry and Walser[3] in 1925. In 1933, Levy and Rousselot[4] recorded 3 instances in young adults. Levy and Von Glahn,[5] in 1944, reported 10 cases in detail and collected a total of 14 from the literature. During the past ten years we have observed 5 more cases at the Presbyterian Hospital in New York and have assembled 20 from published reports. Material from both sources has been included only when none of the commonly recognized causes of heart disease was involved, an adequate clinical description was given, and the diagnosis was established by autopsy.

As yet, no light has been thrown on the etiology. Various names have been applied to the condition. To indicate the obscurity of the cause and because an enlarged heart is at the center of the picture, it is suggested that a proper descriptive term is "idiopathic cardiomegaly."

Incidence.—That the syndrome is not a common one is apparent from the paucity of reported cases and our own experience. During the ten-year period, 1944 to 1953, there were 186,058 admissions to the Presbyterian Hospital and 3,154 autopsies were performed in the Department of Pathology. In that decade, "idiopathic cardiac hypertrophy" was the final clinical diagnosis in only

Presidential address, read at the Sixty-Seventh Meeting of the American Clinical and Climatological Association, Lake Placid, New York, Oct. 14, 1954.

14 patients. Autopsy was performed on 7 of these and the diagnosis was confirmed in 5; in 2, death was ascribed to coronary heart disease (Table I).

TABLE I. INCIDENCE OF IDIOPATHIC CARDIOMEGALY, PRESBYTERIAN HOSPITAL, NEW YORK: 1944-1953 INCLUSIVE

Total number of admissions			186,058
Total number of autopsies			3,154
Number of cases with final diagnosis of "cardiac hypertrophy of obscure cause"			14
Autopsy performed		7	
Diagnosis confirmed	5		
Diagnosis not confirmed (coronary heart disease found in both)	2		
Autopsy not performed		7	
Died in another hospital	1		
Could not be followed	6		

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Clinical Features.—It appears, from analysis of the more recent material, that the condition was more common in males than in females. There was a greater proportion of Negroes than might be expected on the basis of distribution of the two races in the usual hospital population. The age at death ranged from 18 to 69 years; but only 2 patients were over 44. The duration of life, from the onset of symptoms to death, ranged from three weeks to four years; only 3 patients lived longer than two years. Embolization to lungs or other organs was noted in a majority. All the patients suffered from cardiac insufficiency. Most of them failed gradually; some died suddenly.

The electrocardiogram was always abnormal, showing nonspecific changes indicating varying degrees of myocardial damage. Different types of arrhythmia were recorded. In several instances bundle branch block was present, either as a transient occurrence or permanently.

Fever was not a characteristic manifestation. When present it usually could be explained by the presence of a complicating factor. Serologic tests for syphilis were negative except in one instance.

The diagnosis was made in part by the features described and in part by observing a large, failing heart without evidence of the usual causes of cardiac disease. The most frequent mistaken diagnoses were coronary heart disease and pericarditis with effusion.

Pathology.—At autopsy, the weight of the heart in 23 cases ranged from 450 to 1150 grams; the average was 619 grams. Intracardiac thrombi were present in the majority, and emboli to lungs, kidneys, and spleen were frequent. Microscopically, there was hypertrophy of cardiac muscle fibers in all. In different specimens there were observed, in varying degree, areas of interstitial fibrosis; fragmentation, necrosis, and vacuolization of individual fibers; foci of lymphocytes beneath thrombi and endocardium; small patches of slight endocardial thickening, usually beneath thrombi; and rare groups of chronic inflammatory cells around small blood vessels and nerves.

In no instance were there lesions in the heart or other organs which could be ascribed to syphilis. Aschoff bodies were not found in any specimen of heart muscle.

ILLUSTRATIVE CASES

The histories and autopsy protocols of 3 patients will be briefly given to illustrate specific points. I am indebted to Dr. Robert W. Coon, of the Department of Pathology, for the notes on microscopy.

CASE 1.—L. B. was a married white woman who died at the age of 28 years. She first noted symptoms of cardiac insufficiency three years before death, after the birth of her second child. Various physicians had made diagnoses of rheumatic heart disease, of pericardial effusion, and of a congenital cardiac anomaly. There were episodes of pulmonary edema and infarction of the lungs with gradually progressive congestive failure.

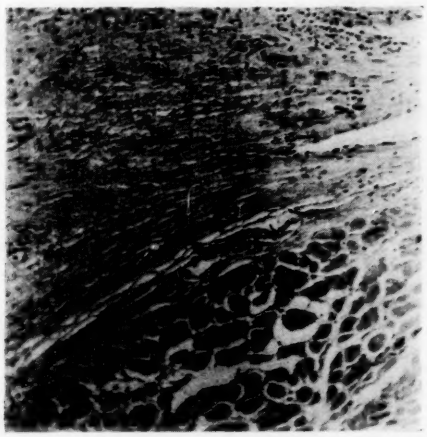

Fig. 1.—Case 1. Hypertrophy of muscle fibers with area of fibrous replacement beneath mural thrombus.

At autopsy the heart weighed 525 grams. Mural thrombi were present in both ventricles. There were pulmonary infarcts in the lower lobes of both lungs. Microscopically, the myocardial fibers throughout were hypertrophied, and there were focal areas of scarring (Fig. 1). Small, scattered foci of lymphocytes were seen beneath the endocardium and in the myocardium, even at some distance from the mural thrombi. The unusual point of interest was the presence of small groups of polymorphonuclear leukocytes and mononuclear phagocytes, suggesting reaction to an inflammatory process.

CASE 2.—V. B. was an unmarried Negro girl, aged 19 years, whose duration of life from onset of symptoms to death was two years. The heart weighed 550 grams. The endocardium of the left atrium was grossly thickened and roughened above the mitral valve. The mitral leaflets were thickened and opaque, as were their chordae tendineae. The other valves were delicate. Microscopically, the myocardial fibers were hypertrophied, and there were numerous fibrous scars. The mitral valve was thickened and fibrotic, and showed a few small capillaries.

The lesions in the heart muscle and mitral valve might well represent the result of previous rheumatic infection. Pathologists disagree as to whether myocardial fibrosis can result from the rheumatic process. But the small amount of scarring in the myocardium and the slight degree of mitral regurgitation are not sufficient to account for such marked cardiac enlargement in a slender girl of 19.

CASE 3.—C. E. S. was a white man, aged 48 years, who died in congestive failure four months after the onset of symptoms and four days after entering the hospital. The electrocardiogram showed left bundle branch block and changes suggesting posterolateral infarction. The final clinical diagnosis, however, was idiopathic cardiac hypertrophy.

At autopsy the heart weighed 900 grams. There was well-marked sclerosis of all the coronary arteries. In the distal portions the lumina were narrowed. The posterolateral wall of the left ventricle was the seat of recent infarction, and a mural thrombus covered this area. The heart valves were normal. Microscopically, the muscle fibers were hypertrophied and there were areas of interstitial fibrosis. About the area of infarction there were scattered erythrocytes and inflammatory cells.

Because of the presence of advanced coronary sclerosis and of myocardial infarction, this case cannot rightly be included in a group characterized by the absence of obvious cause for cardiomegaly. However, it is extremely rare to find a heart enlarged to this degree as a result of coronary atheroma alone.

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In summary, this relatively small group of cases represents a distinct clinical and pathologic entity. The condition is not congenital, for we have observed two patients in whom the heart was normal in size, by x-ray examination, several years before death. There is no demonstrable connection between any specific infection and cardiac hypertrophy in the histories of these patients. Syphilis certainly is not concerned. We have not encountered a familial form, as described by Evans.[6]

The cause of the hypertrophy, then, remains obscure. Apparently there can be an association between massive enlargement of the heart and other conditions, such as rheumatic fever and coronary atherosclerosis; but the question as to whether the relationship is other than coincidental remains unanswered. It is possible that these cases represent a single disease picture observed at different stages of its development, or that they are of varied origin. The diagnosis is made largely by exclusion. The prognosis is poor, for once symptoms have appeared, the duration of life is usually not more than two years, with progressive cardiac insufficiency or sudden death as the terminal event.

It is a rather somber "likeness" that has been delineated. And so, by way of contrast and at the risk of injecting a personal note into these remarks, I propose to relate an episode which left an indelible mark on my memory.

It has been my good fortune to enjoy, since college days, the friendship of Francis Trudeau. The incident to which I refer occurred when we were first-year medical students at The Johns Hopkins University and concerns Francis' distinguished father, Dr. Edward L. Trudeau, whose fame and achievements have brought glory to this Adirondack region. Dr. Trudeau had been elected president of the Congress of American Physicians and Surgeons, an organization now out of existence but then composed of the most prominent members of the profession. The meeting that year was to be held in Washington and, on the way down from Saranac, Dr. and Mrs. Trudeau planned to visit their son in Baltimore. Soon after their arrival Dr. Trudeau, who throughout his adult life was plagued by the tubercle bacillus, showed an elevation of temperature. In spite of feeling ill, he insisted on going on to Washington and I was invited to accompany the family in the role of an aide. It was a proud moment for one who was just beginning his medical studies. But an even greater thrill

was experienced on the following day when we sat with Mrs. Trudeau in the front row of the hall while the president, weak and feverish, delivered his address. It was entitled "The Value of Optimism in Medicine." Several months later, a reprint arrived, inscribed simply—"This is to remind you of the evening in Washington. E. L. Trudeau." It is one of my valued possessions.

A few sentences taken from that address, given on May 2, 1910, will make clearer the meaning of the title: "To the practising physician and surgeon optimism is even more necessary than to the scientist, for besides moulding the doctor's character and guiding him in his decisions as to the case, his optimism is at once reflected to the patient and influences his condition accordingly. How great this influence may be we are learning more and more to appreciate. In his hour of need the patient has no means of judging of the physician's intellectual attainments; it is the faith that radiates from the doctor's personality that he seizes upon and that is helpful to him."

Optimism assuredly is one of those intangible ingredients which, when mixed in the proper proportions, go into the making of a good doctor. But it is the total character that defines the individual; and the core of character is honesty, not only in relationships with others but in appraisal of oneself.

In his daily work, the practitioner is faced with a number of paradoxes. On occasion, he must proceed with promptness and vigor; at other times, considered delay is the wiser course. He must show firmness, yielding only when compromise will avoid petty frictions. He should be sympathetic; on the other hand, humor may save an awkward situation. He must tell the truth as he sees it, but not always the whole truth. His knowledge often is incomplete; yet, regardless of its imperfections, he must act. It is his creed to serve, as best he can, those who seek his aid. And so he must be, above all else, a *cardiomegalic;* for a big heart and humanity are inseparable.

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THE NATURAL HISTORY OF SYSTEMIC LUPUS ERYTHEMATOSUS: AN APPROACH TO ITS STUDY THROUGH CHRONIC BIOLOGIC FALSE POSITIVE REACTORS

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(Received for publication Dec. 1, 1954.)

IN LATE 1948, there was begun a clinical investigation with one immediate and another more remote aim:

1. To investigate the validity of the treponemal immobilization (TPI) test (Nelson and Mayer[1]) in the differentiation of supposed biologic false positive (BFP) reactions from the seropositive tests with standard (lipid antigens) serologic tests for syphilis (STS) occurring in syphilitic infection.

2. To study the phenomenon of biologic false positivity, and to investigate its etiological background.

The opportunity for investigation of the first of these problems is unique to the United States, since from 1938 to the present time, as a part of public health effort to control syphilis, a mass blood testing program has been applied on a vast scale not attempted elsewhere in the world. In the course of this program, many seropositive reactors have been discovered in whom clinical evidence for syphilitic infection was completely lacking.

THE VALIDITY OF THE TPI TEST IN RECOGNITION OF THE BFP PHENOMENON

The application of the TPI test to the recognition of the BFP phenomenon was originally briefly described by Nelson and his associates[2] in 1950; and this information was considerably amplified by Moore and Mohr[3] in 1952. The immunologic details are outlined in this latter paper, and for lack of space will not be repeated here, although more recent studies expanding and verifying earlier conclusions will be briefly described.

Since some of the concepts of biologic false positivity have been challenged by competent observers, it will eventually be necessary to publish in detail a

This investigation has been supported by grants-in-aid from the National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare.

large amount of accumulated but hitherto unreported serologic data. For the purpose of this paper, such detailed documentation is not desirable.

Two points, however, are vital to accurate delineation of the clinical material: the specificity of the TPI test and its reproducibility. On these points there is new and encouraging information.

The Specificity of the TPI Test.—Zellmann,[4] from this clinic, has re-examined this point in detail, utilizing the results in 901 patients tested in the Johns Hopkins laboratories, and 2,778 others collected from the world literature. His conclusions, briefly stated, are that under the best of technical conditions, and *considering the test results of a single specimen only:*

1. The TPI test is nearly uniformly negative (99.7 per cent) in normal persons and in those suffering from other diseases than syphilis.

2. It is nearly uniformly positive (at least 99 per cent) in any stage of untreated syphilitic infection, from secondary syphilis through the balance of the patient's life.

3. In treated early syphilis (primary or secondary) the TPI antibody may permanently disappear from the serum, as does reagin, but at a slower rate and in a smaller proportion of cases than does reagin.

4. In treated late symptomatic acquired syphilis, the TPI antibody persists indefinitely, and probably for a lifetime, in at least 89 per cent of the cases.

6. Since the behavior of reagin in treated latent syphilis is essentially identical with that in treated early or late symptomatic syphilis, it is reasonable to assume that the behavior of the TPI antibody in the two forms of infection (latent and symptomatic) is likewise identical.

7. A valid negative TPI result, once repeated on separate specimens of serum, is capable of differentiating between syphilitic infection and the biologic false positive (BFP) phenomenon, regardless of the factor of previous antisyphilitic treatment, provided that:

   (a) treated early syphilis is excluded
   (b) definite clinical evidence of syphilis (especially tabes dorsalis and congenital syphilis) is excluded.

8. The margin of error in recognition of the BFP phenomenon by means of the TPI test, with the exclusions noted previously, is probably about 2 per cent. Even this can be further minimized by careful epidemiologic examination of family and sex contacts.

The Reproducibility of the TPI Test.—This point has also been studied by Zellmann[5] (data as yet unpublished) in 343 patients from our own clinic, each of whom had from two to six TPI tests performed on *separate* specimens of serum, collected at varying intervals of time over a five-year period. There was complete agreement between all specimens in 86.1 per cent of the patients. Some disagreement was present in 13.9 per cent (48 patients), but in 29 of these, the diagnosis was clinically verified, remotely treated early or late syphilis, and the disagreement was almost certainly due to the factor of low antibody titer. In the remaining 19 cases, the discrepancy was usually minor (negative-doubtful or the reverse) and was not troublesome from the clinical point of view. In

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only 5 of the total 343 cases (1.4 per cent) did the discrepant TPI results encountered present real diagnostic problems.

These data must be interpreted in the light of the high degree of specificity encountered in the testing of a *single* specimen (see above) and of the clinical evidence. So considered, they confirm the conclusion gained from the specificity study, that the margin of error in recognition of the BFP phenomenon by means of the TPI test is 2 per cent or less.

THE BFP PHENOMENON: ACUTE AND CHRONIC

Types of BFP Reactors.—Moore and Mohr[3] established the concept that there are two types of BFP reactors: "acute" and "chronic." The acute variety is characterized by its appearance during or shortly after any one of a wide variety of acute infectious diseases of varying etiology, and by its spontaneous disappearance (reversal to seronegativity) within a short time (a few days, weeks, or months—rarely if ever exceeding six months) after subsidence of the causative acute illness. The chronic variety, on the other hand, is characterized by the facts that there is no identifiable acute infection as a precipitating cause, and that seropositivity with standard STS does not spontaneously disappear, but instead persists for many years, perhaps even for a lifetime.

The technical aspects of the study once accomplished, i.e., the fact that the BFP phenomenon was diagnostically verifiable by means of the TPI test, there arose at once the clinical problem of the etiological background of biologic false positivity. As to the acute BFP phenomenon, this was not of great practical importance, since the cause and effect relationship of acute infectious disease is clear and well established, and since serologic positivity is transitory. (The mechanism by which the acute BFP reaction is produced, of theoretical rather than of clinically practical importance, is still unsolved, although presumably it has to do with a transitory alteration in serum globulin—see below.)

The etiological background of the chronic BFP phenomenon was, in 1948-1949, nearly completely unknown. Only two bits of information were at hand: (a) it is frequent in leprosy, the only identified and identifiable infectious disease known to cause it (a point, incidentally, of no practical importance in the United States, where leprosy is extremely rare, and where it cannot be incriminated as a factor in any of our BFP reactors); (b) a small proportion (exact percentage unknown) of patients with systemic lupus erythematosus (SLE) were thought to be (although, because of lack of availability of the TPI test, in no cases then reported verified as) chronic BFP reactors.

The Frequency of the BFP Phenomenon.—In the initial studies of Moore and Mohr[3] the TPI test was routinely applied to the differentiation of latent syphilis from the chronic BFP phenomenon. The first prerequisite for admission of a patient to this part of the study was that he or she had been routinely discovered to have a positive standard STS known to have been present for at least one year, in the absence of any history of infection with syphilis, and of any physical evidence of the disease; and that his spinal fluid was normal.*

*Note the deliberate absence from this definition of any statement regarding opportunity for infection with syphilis and of epidemiologic verification of this, a point which we now and previously stress (see below) as desirable in the definition of BFP reactors.

In the particular population group under investigation (about 500 white private patients of upper educational and socioeconomic level), 40 per cent of such routinely discovered seropositive reactors were shown by means of negative TPI tests not to have syphilis, but instead to be chronic BFP reactors.*

THE CHRONIC BFP REACTOR: STATEMENT OF THE PROBLEM

We were presented, six years ago, with a then unsolved clinical problem of the etiological background of the chronic BFP phenomenon. There seemed no way to approach this except by detailed clinical and laboratory study of the patients involved, on a long-term basis covering years of periodic observation of members of the group.

In the original report by Moore and Mohr,[3] it was hinted that collagen vascular disease, especially SLE, might bear a causative relationship to the chronic BFP phenomenon; and this opinion was to some extent amplified and documented in preliminary fashion in a second paper by Moore and Mohr,[10] later in 1952.

Several years of additional experience have strengthened this point of view. It is the purpose of this paper to present the developing information.

Although this study has so far been in progress for six years, it is still neither possible nor desirable to present the results in full detail, for two reasons. The first limitation is that of space. So much information, both positive and negative, has accumulated as to require its eventual publication in a series of papers, and perhaps finally in monographic form. Second, and paradoxically, so little information is as yet available (as will gradually appear in this text) that the data of this paper must still be regarded as preliminary, and subject to significant amplification after several more years, perhaps even a decade or two, of further investigation. Only the major positive facts will be dealt with now, with a discussion of their implications.

DEFINITION OF CLINICAL MATERIAL

The point of a patient's entry into this part of the study is the routine discovery of a positive standard STS in an individual with no history of infection with syphilis; with (in most cases) no reasonable opportunity for exposure to such infection, whether congenital or acquired, and with this absence of exposure epidemiologically verified (in most cases) by examination of family and sex contacts; with no evidence of syphilis discoverable on physical examination; and with the absence of syphilis and the presence of the BFP phenomenon verified by at least two negative TPI tests on separate specimens of serum. In order to distinguish acute from chronic BFP reactors, all patients included must have been known to be seropositive with standard techniques for at least one year.

Most of the 148 chronic BFP reactors of this paper were first discovered to have positive standard STS in purely routine fashion (by premarital, prenatal,

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*The approximate 40 per cent incidence of BFP reactors among white persons fulfilling the qualifications briefly described above has been confirmed by at least four other observers—Nelson[6] in a U. S. Navy study; Miller and Hill[7] in New York; Miller[8] in Canada; and Curtis[9] in Michigan.

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or pre-employment serologic testing, on volunteering as donors for transfusion, in the Armed Services), and at the time regarded themselves as completely healthy. The remainder had consulted a physician for one or another cause, including such variable complaints as headache, fatigue, abdominal distress, nervousness, gynecologic complaints, and a wide scattering of others which, at first glance, appeared to bear no relationship to the chronic BFP phenomenon.*

Some of the patients had received antisyphilitic treatment; some had not; but in no case was this treatment given for early infectious syphilis. In view of the demonstration (see above) that TPI antibody persists for a lifetime in treated late syphilis, the factor of previous antisyphilitic treatment could be safely disregarded with only a small probable margin of error.

For reasons given in previous publications,[3,10] all persons included in this series are white private patients of upper educational and socioeconomic level.

METHOD OF STUDY

All patients were subjected to medical history and physical examination; and these, with laboratory surveys and radiologic examinations as indicated, have been repeated as nearly as possible at annual intervals. Laboratory studies were at first conducted on a trial and error basis, those providing consistently negative results (e.g., bacterial agglutination tests, liver function tests, determination of blood electrolytes) being gradually dropped as unproductive of useful information. At present, pertinent laboratory studies are those of urine (with renal function determinations when indicated), and blood (hematologic, serologic, and chemical, with the latter interest chiefly centering around serum globulins).

RESULTS: CLINICAL DATA

As of Nov. 1, 1954, 148 identified chronic BFP reactors had been admitted to the study. These patients have been under repeated personal clinical observation for a minimum of one and a maximum of twenty years, the average observation period being about six years. Of the total 148, 123 have been examined in sufficient detail from clinical and laboratory points of view (many of them on multiple occasions) to justify an opinion as to their clinical status in 1954. These data are presented in Table I.

It is at once apparent that in this material, the chronic BFP phenomenon has been observed predominantly in females (70 per cent). Not shown in tabular form is the further fact that the phenomenon may be one of relative youth: about one-half of the females and one-quarter of the males were first identified as seroreactors under the age of 25; and it was a rarity for first identification to occur after the age of 50.† This is not necessarily the actual sex and age distribution of the chronic BFP phenomenon, since data are lacking as to sex and

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*In only 4 of 148 patients so far studied was this statement not true. Of these, one was first identified as a chronic BFP reactor in the midst of full-blown SLE, one had Still's disease, another rheumatoid arthritis, and another "palindromic" arthritis at time of entry into the series.

†This is the same approximate sex and age distribution as in several large series of patients with verified SLE.

age in the total serologically tested population group from which these cases are drawn.

TABLE I. ETIOLOGICAL BACKGROUND (CLINICAL) IN 148 CHRONIC BFP REACTORS (AS OF NOV. 1, 1954)

SEX	TOTAL CASES	SLE PROVED	RHEUMATOID ARTHRITIS	CVD* PROBABLE	BIZARRE UNDIAGNOSED SERIOUS ILLNESS	CLINICALLY NORMAL		
						DGG†	BFP ONLY	CHEMISTRIES NOT STUDIED
Male	44	1	1	9	3	18	6	6
			25%					
Female	104	9	6	36	2	25	7	19
			49.0%					
Total	148	10	7	45	5	43	13	25
			41.9%					

*Collagen vascular disease (usually SLE).
†Dysgammaglobulinemia.

As to the clinical diagnoses involved, it must be recalled that at the time of discovery of the first positive standard STS, two-thirds of the patients of this series regarded themselves as in perfect health; and in the remaining one-third, the presenting complaints of illness were, in general, minor and not pertinent to the eventual diagnoses listed in Table I. The symptoms and/or physical and laboratory signs which justify the definite or tentative diagnoses of Table I have developed since the first discovery of seropositivity, in episodic, remittent fashion, punctuated in most instances by longer or shorter periods of remission drawn out over a period of years, and permitting diagnostic conclusions only as episode after episode accumulated.

The data of Table I indicate further that the chronic BFP phenomenon apparently has a more serious immediate (within the first few years after its discovery) prognostic import for females than for males. Actually or potentially alarming signs of illness of any form have appeared in only 31.8 per cent of the males and in 51 per cent of the females.

As to the definite diagnoses presented in Table I, only one of the 44 males, in contrast to 9 of the 104 females (8.6 per cent), has developed verified SLE (i.e., verified by clinical picture plus the appearance of the L.E. cell phenomenon in the blood; and by autopsy also, in 2 cases, the only fatalities to date). As will presently appear from some of the representative case histories to be briefly presented in life-table form, the L.E. cell phenomenon seems usually to be a late development, appearing only after some years of episodic illness.

One male (2.2 per cent) and 6 females (5.7 per cent) have developed rheumatoid arthritis, usually mild. This illness is perhaps, in these cases, the first and so far only manifestation of SLE, although this is as yet far from certain.

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Forty-five cases have been listed as probable collagen vascular disease (CVD), i.e., "possible" or "probable" SLE. These diagnoses are on clinical grounds only, since in none has the diagnosis been verified by the L.E. cell phenomenon, biopsy, or autopsy. Such a diagnostic categorization requires preliminary comment followed by documentation.

The disease picture to which the name SLE has been attached is made up, as one might expect, of a wide variety of clinical manifestations reflecting the widespread pathologic involvement of collagen and vascular tissue which may attack almost any part of the body. Indeed, these may be as protean (and as episodic) in nature as the damage done over a period of years by syphilis. Many recent publications on the subject of acute SLE have recorded and analyzed these clinical manifestations. Nevertheless, and at the risk of unnecessary repetition, the more important of them are here listed in Table II, not in order of their probable frequency, since this is, we believe, as yet unknown.

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TABLE II. THE MAJOR CLINICAL MANIFESTATIONS OF SLE*

Arthritis and/or arthralgia, often minor and limited to the small joints of the hands
Fever, otherwise unexplained; often prolonged and low-grade; often episodic; sometimes remittent or intermittent high temperature
Malaise and fatigability, so significant as to constitute a major complaint
Mucocutaneous lesions; sometimes discoid L.E.; more often bizarre
Ocular lesions, various; not always the characteristic cytoid body; but usually involving the posterior uveal tract
Splenomegaly
Serositis; pleuritis and/or pericarditis
Hemorrhagic phenomena; purpura (not always thrombocytopenic); anemia
Convulsive seizures
Psychoses
Cold sensitivity; vasospasm; Raynaud's phenomenon
Photosensitivity
Subcutaneous nodules
Hematuria; nephritis
Phlebothrombosis, major, unexplained by infection, trauma
Pneumonitis
Hypersensitivity, major, especially to drugs
Verrucous (Libman-Sacks) endocarditis

*Not listed in order of frequency.

Of the 45 cases listed in Table I as probable CVD, 21 are classified as "probable" and 24 as "possible" SLE. The clinical manifestations in 21 patients classified as "probable" SLE are listed in Table III, and in 24 patients regarded as "possible" SLE in Table IV. Not appearing in either of these tables are supporting laboratory data. L.E. cells have so far been demonstrated in none of these. Disorders of gamma globulin (see below) are present in most of them; and hematologic changes (also see below) in the majority, and these, when present, lend further weight to the clinical suspicion. It will be noted that the difference

between "possible" and "probable" SLE lies chiefly in the average number of separate episodes of illness in the two groups: 2.7 per patient in the "possible" group; nearly 3.6 per patient in the "probables."

TABLE III. "PROBABLE" SLE: CLINICAL MANIFESTATIONS IN 21 PATIENTS

SYMPTOM AND/OR SIGN	NUMBER OF CASES SHOWING SPECIFIED SYMPTOM OR SIGN
Fever	12
Arthralgia and/or arthritis	13
Ocular lesions	6
Splenomegaly; serositis; cutaneous lesions	5 each
Reynaud's phenomenon; significant malaise	4 each
Major phlebothrombosis; psychoses; nephritis	3 each
Photosensitivity; mucosal lesions; chorea; hematuria	2 each
Thrombocytopenic purpura; convulsions; nephritis	1 each

Each patient has had at least 2 and usually several of the 17 manifestations listed; and the 21 patients have had a total of 75 of these symptoms and/or signs (i.e., 3.57 per patient).

TABLE IV. "POSSIBLE" SLE: CLINICAL MANIFESTATIONS IN 24 PATIENTS

SYMPTOM AND/OR SIGN	NUMBER OF CASES SHOWING SPECIFIED SYMPTOM OR SIGN
Arthralgia and/or arthritis	18
Fever	10
Malaise, significant	12
Mucocutaneous lesions	8
Psychoses	5
Purpura (not thrombocytopenic); convulsions; ocular lesions	3 each
Subcutaneous nodules; paroxysmal tachycardia; hepatomegaly; serositis; nephritis	1 each

These 24 patients have had 65 such episodes of illness (i.e., 2.7 per patient).

Perhaps a better idea of the evidence on which the diagnoses of possible, probable, and verified SLE have been based may appear from a representative

(but far from inclusive) series of thumbnail life tables of individual patients, here reproduced as Tables V to IX.

TABLE V

J. H. H. #520441 C. L. ADM. 1949 W 21 F

AGE IN YEARS	EVENT
18 (1946)	Routine STS negative
21 (July, 1949)	Pregnant. Routine STS positive
21 (Sept., 1949)	*Depressive psychosis:* shock therapy. *Mild toxemia*
21 (Nov., 1949)	Psychosis continues; therapeutic abortion at 5½ mo. *Cytoid body rt. eye*
21 (Dec., 1949)	Aortic insufficiency (heart normal several observers 6 mo. earlier). *Libman-Sacks endocarditis* suspected
22 (Jan., 1950)	STS 4 U. CSF 0. TPI 0. CF 3+; T.T. 10.3; glob. 2.2 Marrow: — no L.E. cells
24 (Oct., 1952)	Pregnant 2 mo. *Chorea gravidarum.* Therapeutic abortion
25 (May, 1953)	Clinically well; AI unchanged. STS wk.pos. TPI 0. DGG. *Albuminuria.* CSR* 30
25 (June, 1953)	*Polyarthralgia and arthritis fingers* after sunlight. *Photosensitivity*
26 (Dec., 1954)	Clinically well. *L.E. cells repeatedly + past 18 mo.*

SLE (moderately severe course 5½ yr.; well now)

*Corrected sedimentation rate.

TABLE VI

A. C. G. ADM. 1941 W 24 F

AGE IN YEARS	EVENT
24 (1941)	U. R. I. STS +
24 (3 mo. later)	P.E. 0. STS: WaR 18 u.; flocs. 4 u.
26 (Jan., 1943)	Pregnant 2 mo. *Toxemia.* Miscarriage at 5 mo. 10 days later *severe jacksonian fit*
32 (1949)	Pregnant; mild toxemia. Normal child
32-34	Fleeting *polyarthralgia* and *arthritis fingers*, lasting 2 yr.
34 (1951)	Pregnant. PE 0. STS +. TPI 0. Mild microcytic *anemia.* CSR 30. CF 4+. T.T. 5.9 Glob. 2.5 L.E. cells 0
36 (1953)	Pregnant. No toxemia. Normal child
31-36	Raynaud's disease (fingers)
36 (Feb., 1954)	Postauricular lymph nodes; otherwise 0. Not now anemic, W.B.C. 2700. STS: WaR 64 u., flocs. 4 u. TPI 0. CF 4+. T.T. 6.0 Glob. 3.7. *L.E. cells* +

SLE (12-year course from first discovery seropositivity; patient well 1954)

In the present material, there are no observed examples of three other diseases commonly included in the collagen vascular disease group: periarteritis nodosa, scleroderma, and dermatomyositis.

Five patients of Table I are listed as having bizarre undiagnosed serious illness. Two of these (Cases 2 and 4 below) have been reported in detail in another paper.[11] Of all of them, it may be said that the underlying disorders,

whatever they may be, have so far defied the diagnostic acumen not only of ourselves but also of consultants in our own and other hospitals. Their illnesses, all chronic, may be briefly described as follows:

Case 1. Female, aged 30 at onset. Homonymous hemianopsia, unexplained, persisting unchanged and without further developments over a 10-year period.

Case 2. Male, aged 61. Bilateral orbital granulomas, cause undetermined; 18 months' duration, responding to ACTH. BFP reactor in both blood and cerebrospinal fluid.

TABLE VII

J. H. H. #435056 M. S. J. ADM. 1947 W 23 F

AGE IN YEARS	EVENT
15 (1938)	STS +. Virgin. Family nonsyphilitic. No treatment
21 (1944)	STS +. No treatment
22-23 (1945-1946)	*Intermittent fever* 15 mo. T. 101-103. 13 lb. *wt. loss.* No diagnosis made elsewhere
23 (1947)	PE 0. STS 16 u. CSF 0. Mild normocytic *anemia.* *Leukopenia* (3200). *CSR 22. CF 4+. T.T. 15.0* Serum glob. 2.5. No diagnosis
26-30 (1950-1953)	Intermittent recurrent *subcutaneous nodules.* Mild *arthritis* fingers
27-30 (1951-1953)	Albuminuria; recurrent *edema* with variable *azotemia.* Anemia, leukopenia, DGG, + STS persist
29 (Oct., 1952)	*Pleuritis; pneumonitis* l. base
29 (Nov., 1952)	Long-standing GI distress (for years). *Unexplained hematemesis* (x-rays 0)
30 (Nov., 1953)	PE: *pleuritis* left base; persistent weight loss. STS + 16 u. TPI: 0. CSR 34. CF 4+. T.T. 8.9 Glob. 2.7. *L.E. cells* +

SLE (15-year course; pt. fairly well 1954)

TABLE VIII

J. H. H. #346936 G. G. ADM. 1945 W 24 F

AGE IN YEARS	EVENT
16 (1937)	? Pleurisy
21 (1942)	*Febrile attacks*, T. 101-103 q. 2-8 wk. lasting 2½ yr. before admission 1945
22 (1943)	*Choroiditis left*
24 (1945)	P.E. 0. STS: WaR + 13 U. All flocs. 0. CSF 0. Serum glob. 3.5 Extensive lab. study otherwise 0. No diagnosis
24-30 (1945-1951)	Febrile attacks continue, lessening in frequency and severity ages 26-32. Attacks disappear during 3 pregnancies this period; recur promptly thereafter. *Splenomegaly* during attacks
32 (1953)	P.E. 0 except old choroiditis. Lab.: *CSR 34.* Mild normocytic anemia. *CF 3+. T.T. 8.6.* Serum *glob. 3.53.* STS: WaR +, flocs. 0, TPI 0 (x 3). L.E. cells 0

SLE Probable (13-year course)

Case 3. Female, aged 47. Multiple cranial nerve lesions, eventually shown to be due to glioma; BFP reactor both in blood and CSF; multiple unexplained severe hematemesis.

Case 4. Male, aged 46. Recurrent severe chorioretinitis, persistent CSF pleocytosis and protein excess, 10 years' duration.

Case 5. Male, aged 38. Fever, arthritis, parotitis, splenomegaly, hepatomegaly, diabetes mellitus (no evidence of sarcoid).

TABLE IX

T. A. G. ADM. 1938 W 26 M

AGE IN YEARS	EVENT
"Childhood"	? *Rheumatic fever*
To age 26	Healthy
26 (1938)	Donor: STS +. CSF 0
26 (1 mo. later)	*Low-grade fever 1 mo. Splenomegaly*
27 (10 mo. later)	Violent abdominal pain; slight fever; exploratory laparotomy 0 except moderate splenomegaly. No biopsy
34 (1946)	*Depressive psychosis* 6 mo.
37 (1949)	*Raynaud's disease* (fingers), persisting
38 (1950)	Severe *serum sickness* after TAT
38-41	? Photosensitivity
41 (May, 1953)	P.E. 0. STS +. TPI 0. No DGG. L.E. cells 0

SLE possible (17-year course)

LABORATORY DATA

Only pertinent positive information will be included here and this in very condensed fashion.

Hematologic Data.—Anemia: Only a rare male (3 per cent) but about 50 per cent of the females were anemic. This was usually a mild to moderate normocytic or microcytic hypochromic anemia in the absence of evidence of blood loss; sometimes constantly, sometimes intermittently, present on repeated examinations over a period of years; sometimes responsive to iron, sometimes not. Four of the females had severe anemia, in two of whom the type was hemolytic. In the females, there was usually no parallelism between the presence or absence of anemia and clinical symptoms.

Leukocytes were usually in the normal range. In a few patients (about 11 per cent) there was occasional or persistent leukopenia, but this was only occasionally striking, even in those with verified SLE. In about 7 per cent there was persistent and unexplained leukocytosis.

Mild to moderate *eosinophilia* (range 4-20 per cent) was present in nearly one-quarter of the patients in whom data are available. This was not necessarily associated with clinical manifestations of the hypersensitive state. Its significance is unknown.

Sedimentation Rate.—In more than one-half of the chronic BFP reactors twice as often in females as in males), the corrected sedimentation rate (Winrobe) was persistently elevated, often strikingly so, over a period of years.

L.E. Cells.—These have been searched for in most of the patients of this series. All smears have been examined by two or more observers (including a member of the Department of Hematology). They have been found in 10 cases.

DYSGAMMAGLOBULINEMIA

As a part of the examination of these chronic BFP reactors, and on the reasonable suspicion that the BFP phenomenon itself is in some way associated with the gamma globulin fraction of serum, there have been routinely performed certain protein flocculation tests (cephalin flocculation, thymol turbidity) and a chemical estimation of serum total protein, albumin, and globulin. In about three-quarters of the patients, electrophoretic patterns were also obtained.

In practically all the patients with some form of clinical disease, and in particular in the 62 who are diagnosed certainly or probably as having collagen vascular disease (Table I), one or more of these tests was abnormal.

In 43 patients of the 148, there was no evidence of any clinical disorder, but abnormalities were present in one, two, three, or all four tests together. The incidence of some abnormality of serum globulin was about 90 per cent of the entire series of patients in whom such tests were performed.

This type of abnormality of protein flocculation tests or serum globulin is not found with regularity in patients with syphilis.

The enormous literature with respect to protein flocculation tests, particularly cephalin flocculation and thymol turbidity tests, indicates that these have been usually used for the detection of hepatic damage. In the first two years of the present study, and in spite of the fact that few, if any, of the patients in question showed any symptoms or signs suggestive of liver disease, the possible relationship of these abnormal protein flocculation tests in this group of patients to the question of liver damage was further investigated by the performance (in more than one-half the patients in the series) of other liver function tests, including particularly Bromsulphalein excretion, and phosphorus and alkaline phosphatase determinations. These were always normal, and have now been discontinued on the ground that the abnormalities of gamma globulin in this series of patients are clearly not related to demonstrable disease of the liver.

DISCUSSION

The results of this study so far available establish a number of facts and point to the strong probability of certain other clinical implications.

The TPI Test.—It is established, we believe, that under the limitations discussed above, the TPI test can be utilized to distinguish the BFP phenomenon from syphilitic infection with a margin of error of about 2 per cent. Unfortunately, the TPI test is a complicated biologic-immunologic procedure, requiring meticulous care in its performance. It is susceptible to technical difficulties which may at times interfere with the validity of results of a given laboratory over a period of weeks. It is time consuming and expensive to perform. It

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provides only qualitative, not quantitative, results, since a satisfactory method of quantitation has not yet been agreed upon. To attempt quantitation, even on a relatively small scale, would enormously increase expense. Perhaps because of the lack of quantitation, there are defects in the reproducibility, which seem to be due largely to low antibody titer in syphilitic infection, especially if the patient has been treated. It does not permit recognition of the BFP phenomenon in a patient who also has syphilis, a combination which may, of course, readily occur.

Because of these defects, the TPI test is clearly unutilizable on anything approaching a service basis comparable to that of standard serologic tests. Only a few laboratories in this country are capable of its performance; in them the number of specimens which can be accepted for diagnostic purposes is sharply limited. None of this, however, impairs its value as an investigative tool.

Studies are in progress in a number of laboratories to simplify the detection of the TPI antibody by means of the much less elaborate agglutination technique, employing killed rather than living Treponema pallida as an antigen. The results of such studies are encouraging, but the simpler tests are not yet ready for wide-scale application. If and when this can be accomplished, it is quite certain that the use of beef heart lipid antigens for the detection of syphilis will be generally abandoned, although paradoxically it will probably be desirable to continue their use for recognition of BFP reactors.

The Incidence of the BFP Phenomenon.—As applied to the population of the United States as a whole, this is unknown. To determine it would require the economically impossible procedure of routine standard serologic testing of several million persons of white and Negro races, both sexes, all ages, from scattered localities, and of varying educational and socioeconomic levels; and with parallel TPI testing of all seropositive reactors discovered in the original survey. The incidence of BFP reactions in particular disease states, e.g., SLE, is a simpler problem, since in each disease condition surveyed, only a few hundred persons would require parallel standard and TPI tests. To study disease entities in this manner would not, however, fulfill the necessities raised by this paper, since the majority of our chronic BFP reactors were in supposed health when their original seropositivity was discovered.

The most which can be said at the moment is that the BFP phenomenon, acute or chronic, is frequent. (The chronic type is far more frequently detected than the acute, since for the latter is required the fortuitous accident of routine serologic testing in direct time relationship to a precipitating infectious disease. The chronic BFP reactor, on the other hand, is more readily recognizable, since his reactivity to lipid antigens persists for years.) The exact frequency depends on the population group under investigation. In this and other series of white patients of upper educational and socioeconomic level, it appears to approximate 40 per cent among routinely discovered seropositive STS reactors. Unpublished information from this hospital (Hahn and Catterall)[12] indicates that in an outpatient clinic population of lower educational and socioeconomic level and in

race approximately 90 per cent Negro, only about 10 per cent of clinically and serologically comparable patients are BFP reactors.*

SLE and the Etiological Background of the Chronic BFP Phenomenon.—The clinical and laboratory data of this study strongly suggest that the chronic BFP phenomenon is one manifestation of tissue injury, probably chiefly of collagen and vascular tissue, due to an unknown agent or antigen.

It is suggested further that one of the first evidences of this is in an as yet unidentified alteration of serum globulin (dysgammaglobulinemia†), whether quantitative, qualitative, or both. It is suggested that this chemical disturbance is responsible for a number of the observed laboratory phenomena: the BFP reaction itself, the increased sedimentation rate, the abnormalities of protein flocculation tests, the quantitative increase in serum globulin, the occasional alteration in electrophoretic pattern of the serum, and the development of the L.E. cell phenomenon. It is suggested, moreover (and we believe that this can be documented in subsequent publications), that these evidences of dysgammaglobulinemia may progress slowly in seriatim fashion. First to appear is perhaps the BFP phenomenon itself,[13] together with or shortly followed by an increase in sedimentation rate and thymol turbidity; still later by strongly positive cephalin flocculation tests and quantitative increase in serum globulin; and much later still, probably not until after several or even many years, a disturbed electrophoretic pattern and the appearance of L.E. cells (cf. Tables V to IX).

It is perhaps unnecessary to emphasize the point that these identical laboratory changes tend to occur with great frequency in established and verified SLE (most recently discussed in detail by Harvey and his associates[14]). Not all of them are always present in the individual case of SLE; and the reason for this is unknown. Why, for example, are only a small proportion (perhaps 20 to 25 per cent) of patients with advanced and verified SLE found to be BFP reactors?

Our material strongly suggests, too, that the laboratory evidences of dysgammaglobulinemia usually, although not necessarily always, precede by months or years (even many years) any clinical developments suggesting disease; and indeed that these laboratory changes may persist for many years in the absence of any detectable clinical disease at all. Nevertheless, clinical disease usually does develop in many chronic BFP reactors; and the phenomenon is far from innocuous.

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*These data might be employed in a theoretical computation. Supposing that one applies routine standard serologic testing to a population group of one million white males and one million white females between the ages of 15 and 50 years, drawn from the Northern group of states in this country (in which the incidence of syphilis, originally comparatively low, is rapidly decreasing). Supposing the incidence of seropositive standard STS reactors among the males to be 4 per cent and among the females 1 per cent. Supposing further that one-half each of males and females are identifiable syphilitics on past or present clinical grounds. Supposing now each of the remainder, routinely discovered to be seropositive, to be checked by the TPI test, one might come up with 10,000 BFP reactors, i.e., 0.5 per cent of the original population tested (probably greater in females than males).

If a similar survey were carried out in a large Negro population in the deep South, one can guess that identifiable BFP reactors would be far fewer in number.

†Abbreviated DGG in tables and text.

Indeed, the physician is no longer justified, when he has identified a chronic BFP reactor, in dismissing his patient with congratulations on the absence of syphilis. Instead, he is faced with a lengthy and detailed clinical investigation to attempt to identify the cause of the BFP reaction; and this may and usually does mean prolonged periodic observation and re-examination.

When disease does develop in these patients, it tends to follow a remarkably uniform pattern, the clinical manifestations of which conform to a series of events known to occur in verified collagen vascular disease, especially SLE. These symptoms and/or signs, described above, are usually episodic, sometimes mild (e.g., no more than minor bouts of fleeting arthralgia or actually demonstrable arthritis in the fingers lasting a few days at a time; a couple of weeks of low-grade unexplained fever); sometimes more portentous (an episode of purpura); sometimes serious. The episodes are usually punctuated by longer or shorter periods of remission, lasting weeks, months, or even many years. A single manifestation (e.g., Raynaud's phenomenon) may persist unchanged for many years—in one female in this series for sixteen years—without further developments. More frequently, one manifestation is followed episodically by another. In one patient of this series, in whom L.E. cells have not yet been found, there occurred rheumatic fever in childhood; then, seriatim over an eighteen-year period, arthritis, unexplained fever, Raynaud's disease, intermittent splenomegaly, a psychosis (with recovery), posterior uveitis, and finally photosensitivity.

This episodic clinical pattern has finally evolved in 10 of the 148 patients of this series into verified SLE: that is, assuming that one accepts, as most observers do, the L.E. phenomenon as essentially limited to SLE, and occurring rarely, if at all, in other conditions. Our material indicates that the L.E. cell phenomenon is probably a late development in SLE, not appearing until other manifestations of the disease have been present, even though intermittently, for some time, in certain cases perhaps for many years.

Seven of the group of 148 (1 of 44 males and 6 of 104 females) have developed rheumatoid arthritis (which may be the first manifestation of SLE) without other clinical developments.

Forty-five of the total (9 of 44 males and 36 of 104 females) have developed episodic clinical illness with manifestations (usually multiple) known to occur in SLE, but as yet without verification.

Nearly one-half of this total group of 148 patients, therefore, has suffered, or now suffers, from a disease syndrome compatible with the diagnosis of verified or potential SLE.

The clinical course of illness in the patients of this series, as exemplified by the 62 patients with verified or presumed SLE (or collagen vascular disease), is an exceedingly chronic one, lasting over a period of years, perhaps in some instances even decades. Deaths have been only two in number, and many patients are surprisingly well as of the last observation, in spite of the multiplicity of manifestations. These facts are illustrated by the several brief case histories provided in tabular form. The long and relatively benign course of the patients of this series is in complete contrast to the usual textbook picture of acute SLE,

which is commonly represented as a uniformly fatal illness of comparatively short duration.

Finally, it is suggested by the present material that SLE is a much more common disorder than has heretofore been thought. The physician's suspicion of the diagnosis should be aroused at once by the isolated appearance of many of the symptoms and/or signs listed in Table II; and should be greatly strengthened if several of these appear in the same patient in episodic fashion.

THE POTENTIAL CONTRIBUTION OF THIS STUDY TO AN UNDERSTANDING OF THE NATURAL HISTORY OF SLE

In such a complex disease picture as that of SLE, the question inevitably arises as to whether all the manifestations usually attributed to it are in fact parts of a single entity, or represent instead a group of related or even unrelated clinical syndromes.

Another important problem, common to chronic disease in general, and especially true of SLE, is an estimate of prognosis. What happens to an affected group of patients in the absence of any specific form of treatment? This information is vital to any subsequent estimate of the possible palliative or curative effect of any form of treatment.

In SLE, the several pertinent papers on this point, reviewed by Merrell and Shulman,[15] attempt an answer to both of these questions by the retrospective analysis of a series of patients, usually hospitalized, with verified SLE. Such patients are questioned as to whether and when the protean manifestations of Table II (plus other minor ones not there listed) occurred. This approach is subject to two fallacies: (1) the fallibility of human memory, since not even such skilled observers as physicians are supposed to be can always recall whether they ever had some of the minor episodes listed, nor to date them correctly if they did occur; (2) such enquiries have never been paralleled by exactly similar questions directed to a comparable group of persons (as to race, age, and sex, for example) who at the moment of study are in apparent health or who suffer from diseases which are clearly *not* SLE. As to prognosis, the duration of life in SLE patients is measured from the variable starting points of verified diagnosis or, much more vaguely, from the date of appearance of the first physical evidence of illness possibly attributable to SLE.

When this method of study is used, the results obtained, as to both points above, are likely to be grossly distorted, especially as to prognosis, in which mortality rates are excessively high and the expected duration of life represented is unusually short.

Merrell and Shulman,[16] in a closely reasoned paper, present a further discussion of the determination of prognosis in chronic disease, illustrated by SLE as exemplified in 99 of the 138 cases reported in monographic form by Harvey and his associates. They have applied the well-known actuarial biostatistical method of life tabling (utilized far too infrequently by physicians). They pointed out that their results as to survivorship are not comparable with experience in SLE reported by other clinics, since such "results have commonly been presented with an inadequate description of the cases and analyzed by

diverse and erroneous methods." Their own 99 patients include 87 in whom the diagnosis of SLE was verified by the demonstration of L.E. cells, biopsy, autopsy, or a combination of these (in 56 of whom the *clinical* diagnosis of SLE was likewise "apparent" and in 31 of whom it was "doubtful"), plus 12 additional "clinically apparent" patients lacking laboratory verification (all of these latter having at least 7 and at times as many as 14 manifestations of SLE). When the date of entry into their study was taken as the date of diagnosis, the estimate of survivorship for 4 plus years was 51 per cent.

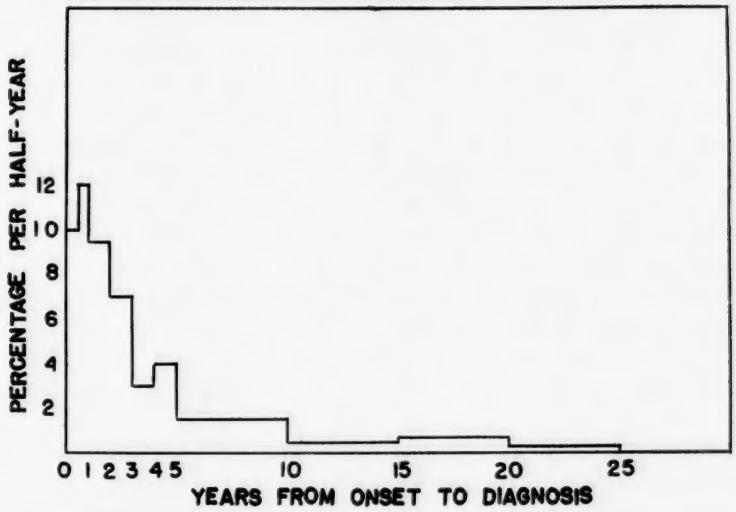

Fig. 1.—Intervals from onset to diagnosis of SLE. (From Merrell, M., and Shulman, L. E.: J. Chron. Dis. 1:12, 1955, published by The C. V. Mosby Company).

Merrell and Shulman have purposely avoided using "date of onset" of symptoms of SLE as a point of entry into their analysis. They said: "There is great uncertainty in dating vague and often subjective first symptoms. . . . Even if we could get an objective definition of onset . . . the cases coming to observation are selected through the omission of similar cases having a similar onset who did not come to the clinic. Those failing to come are so likely to have had a different course of the disease that observed experience cannot be assumed to be representative of cases from onset." They do, however, provide data as to intervals from onset to diagnosis (their Fig. 2, herewith reproduced as Fig. 1). Of this they said: "In case of uncertainty of symptoms of onset we have selected the more definite and recent ones. The duration of time between the estimated onset and the date of diagnosis varied from less than a month to 35 years (averaging 4.9 years), but the distribution is piled up toward the short intervals." This information, even with its inexactness, nevertheless provides a strong indication (considered together with their evidence as to survivorship *after diagnosis*) that the course of SLE is often exceedingly chronic, rather than the

relatively acute one it is usually portrayed to be. Thirty-one of their 99 patients (nearly one-third) had had symptoms attributed to SLE for five or more years before *diagnosis;* and of these, 14 for ten or more years!

The results obtained by Merrell and Shulman are subject to the shortcoming, which they recognize, of the brevity of the observation period from diagnosis, since only those cases are included which were recognized in the years 1949-1953 inclusive. Nevertheless, the probability of survivorship in their series for extended periods of time is considerably greater and the prognosis much better than in other reported series of "verified" SLE analyzed by less accurate statistical methods.

However, the clinical material utilized by Merrell and Shulman has a most important point in common with other similar efforts to define prognosis in SLE, namely, that their own and all other recorded series to date start with a group of patients who were sufficiently ill to seek hospital (and often hospitalized) medical care, and in whom the investigator was satisfied, originally or eventually, that this illness (and subsequent events) was due to SLE, "verified" on clinical grounds by the multiplicity of manifestations, on laboratory grounds, or on both.

(It should be emphasized that the series of 138 patients with SLE reported by Harvey and his group and the 148 patients of this study are *not* identical. Each series includes a very few patients—not more than 10—who are likewise included, for different reasons, in the other.)

In all publications to date, therefore, efforts to study the natural history of SLE in terms of its gradual evolution, and to estimate its progress, are based on patients with what might be called advanced SLE at least far enough advanced to prompt medical care for illness presumably associated with it.

A forward-looking rather than a retrospective study of the natural history of SLE, its evolution, and its prognosis would therefore be highly desirable. Such a study should begin with persons who are clinically well, rather than ill, and trace developments in them from health to illness, and if possible to eventual death. The material of this paper offers precisely this opportunity, provided its major thesis is accepted, i.e., that the chronic BFP phenomenon is often the forerunner of a disease syndrome which conforms to that of SLE. Its starting point is the routine discovery of a laboratory abnormality in persons the majority of whom are in health at the time; and in the minority of whom illness led to the discovery of the positive STS, this was usually due to symptoms other than those of SLE. In them, prolonged periodic observation permits the recording and dating of events as they occur on the basis of actual objective observations by the physician, rather than on the retrospective and often subjective memory of the patient. Coupled with this is the opportunity to record seriatim laboratory data, which, as suggested above, may precede clinical developments by long periods of time.

We anticipate certain entirely pertinent objections:

1. The clinical material is selected on the factor of identification of the chronic BFP phenomenon; and cannot take into account the large number of persons who, likewise being chronic BFP reactors, are not recognized as such.

2. The date of onset of serologic positivity is in all cases unknown. Available only is the date of its first recognition. This is not a serious objection, however, since the date of the first known positive STS corresponds to Merrell and Shulman's "date of diagnosis" of SLE. In our case, the original diagnosis is that of the chronic BFP phenomenon; from this we work *forward* in point of time, while other students of SLE must work *backward* as well as forward, dating from the diagnosis (or onset of clinical symptoms) of that disease.

3. The course of SLE may differ in chronic BFP reactors from that in the much larger number of SLE patients who do not develop this phenomenon. If this is true, it should not be difficult to determine it in the course of time. Merrell and Shulman have suggested that in SLE [as in syphilitic primary optic atrophy], there are "rapid and slow progressors," but the factors which determine the rate of progression are unknown. It may be that the early disorder of serum globulin observed in our chronic BFP reactors is a factor in promoting slow rather than rapid progress; certainly this is suggested by the extreme chronicity of the disease process in our patients and by the (so far) low mortality rate.

4. The study of the course of events in chronic BFP reactors should, of course, be paralleled by an identical study of a group of seronegative persons, comparable as to race, age, sex, and clinical status at the point of their entry into the study group.

Eventually, of course, it will be essential to analyze our material by the life-table method used by Merrell and Shulman, but the time for this is not yet ripe. Several more years of observation of our patients is desirable before such an analysis is made, and at least another decade is probably necessary before our results begin to take final form.

In the meanwhile, another avenue of approach is desirable in our patient material and in other similar patients. This is an immunochemical approach to the nature of the dysgammaglobulinemia and of the tissue injury which causes it. Such studies offer some chance of development of an immunologic test for the early recognition of collagen vascular disease, especially SLE; and may throw some light on its obscure etiology.

SUMMARY AND CONCLUSIONS

1. The chronic BFP (biologically false positive) phenomenon is
   (a) Recognizable, with a probable margin of error of 2 per cent or less, by means of the TPI (treponemal immobilization) test.
   (b) Frequent in occurrence.
   (c) Frequently first discovered as a result of routine blood testing of patients in apparent health.
   (d) Twice as frequent in females as in males, and in both sexes more frequent in younger persons.
   (e) Frequently followed in a few years (especially in females) by the development of verified SLE (systemic lupus erythematosus) (9 of 104 females of this series), or by an episodic form of chronic illness the manifestations of which conform to those known to occur in SLE (52 of 148 total cases of this series).

(f) Frequently accompanied by hematologic disorders.

(g) Even more frequently associated with disorders of serum globulin ("dysgammaglobulinemia").

2. The implications of these facts are discussed.

3. It is pointed out that the continuation of this study over a period of years offers a unique opportunity to study the natural history of SLE in forward-looking rather than in the usual retrospective manner.

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Review

MODERN CONCEPTS OF SYSTEMIC LUPUS ERYTHEMATOSUS: A REVIEW OF 126 CASES

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(Received for publication Nov. 1, 1954.)

IN 1948 and 1949, diagnostic and therapeutic measures were developed in systemic lupus erythematosus (S. L. E.) which aroused considerable initial enthusiasm. No one could tell during that time what the true value of the tests for lupus erythematosus (L. E.) was going to be, nor could the new treatment of the disease with cortisone and corticotrophin be properly evaluated. Sufficient time has now elapsed to estimate the worth of these measures more accurately.

There had been almost 100 years of interest in this disease before the discovery of the L. E. phenomenon* and the development of the diagnostic L. E. tests which were based upon it. The observations made during this time are well documented,[1,a-h] and will not be dealt with here. The present survey is based upon a group of 126 patients with positive L. E. tests, seen since 1948 at the Cleveland Clinic. Nineteen of these were males, one of whom was a 10-year-old boy. The youngest patient was 8, and the oldest was 72 years of age. It is proposed to emphasize some of the atypical features of systemic lupus erythematosus which appeared repeatedly in this group, and to attempt to correlate therapeutic measures used in their correction.

CLINICAL MANIFESTATIONS

Lupus erythematosus was considered to be such a rarity that until recently it had received scant attention at teaching institutions. As a result, many physicians are unaware of the atypical varieties, and unfamilar even with the classic forms of the disease. Because of this, and for subsequent comparison with the irregularities, the accepted standard manifestations of L. E. are presented first.

*Rosettes of leukocytes and L. E. cells, induced by the L. E. plasma factor, in peripheral blood and bone marrow preparations.

Typical Case.—There usually is no difficulty in making a diagnosis in the patient with classic acute disseminated lupus erythematosus. Typically, the patient is a young woman, less than 30 years of age, who is suddenly taken ill, often after a bad sunburn. She is bedridden, with high fever; a striking feature is an erythema which extends across the nose to the cheeks which, as Hebra originally pointed out, resembles a butterfly (Figs. 1-7, 9-11).

Fig. 1.—Disseminated discoidal L. E. without systemic involvement. Negative L. E. tests. Duration twelve years. No response to gold, bismuth, cortisone, corticotrophin, or Atabrine.

Fig. 2.—Same patient as in Fig. 1. Appearance one month after chloroquine.

The patient appears to be utterly exhausted. She is unable to move without fatigue, and without pain in the muscles and joints. The mouth may show moniliasis or extensive ulceration but, even without this, she has a distaste for food. She is unaccountably and severely ill.

Except for the fever, prostration, and butterfly erythema, the general physical examination often reveals very little. The pulse rate may be 120 per minute

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or higher. The blood pressure is usually hypotensive. There may be a pericardial or pleural friction rub, and fluid may be present. Gallop rhythm is sometimes present. The liver edge is frequently down two or three fingers. Lymph nodes and the spleen may be palpable. The laboratory studies classically reveal the hemoglobin to be 8 to 9 Gm. per 100 c.c. The leukocyte count

Fig. 3.—Disseminated discoidal L. E. followed by systemic involvement. Positive L. E. tests. Occasional acute flare-ups respond to steroidal therapy. Skin failed to improve to any of previously mentioned medications.

Fig. 4.—Discoidal L. E. lesions appearing in acute systemic L. E. after prolonged steroidal remission.

is between 2,000 and 3,000 with a surprisingly normal differential count. Almost invariably in the severe, untreated case, there are no eosinophils. (After steroidal therapy is started, the eosinophils may *increase*, a paradox exclusive to L. E.) The sedimentation rate is elevated, often out of all proportion to the

Fig. 5.—Discoidal L. E., eleven years' duration. Weakly positive L. E. tests associated with low-grade illness. L. E. tests usually negative.

Fig. 6.—"Lymphocytic" L. E. simulating acute L. E. Negative L. E. tests. Steroids contraindicated. No systemic manifestations.

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degree of illness. The L. E. test is positive by any established technique. The urinalysis may be normal or may show microscopic hematuria, casts, and albuminuria of varying degree. The urinary sediment resembles a mixture from all the stages of glomerulonephritis.[2]

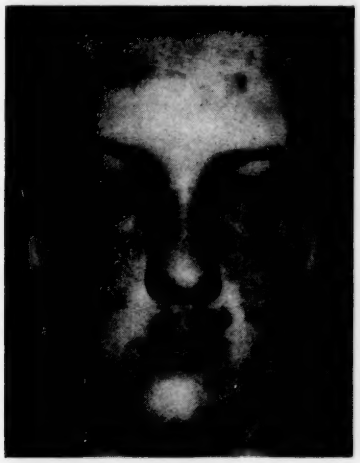

Fig. 7.—Patient with every appearance of "acute disseminated" L. E., except had negative L. E. tests Steroids withheld. Gradual improvement.

The Lupus Diathesis.—The patient's past history may reveal perfect health. More often, there is evidence of a predisposition to the disease, that is, a lupus diathesis, akin to the rheumatic diathesis. A clue to this predisposition is noted in many ways. A peculiar sensitivity to infection has long been recognized. An ordinary sore throat, a tuberculin test, a tooth extraction, or even routine immunologic testing[3,a,b] may have precipitated the illness. Frequent attacks of pneumonia are not uncommon in the history. The patient may have received antisyphilitic treatment given because of what subsequently proved to be biologic false positive serologic tests for syphilis. She may have had idiopathic epilepsy for years. Instead of the sudden, explosive onset there may have been a long period of low-grade, chronic ill health, during which time the patient was neither sick enough to be bedridden, nor well enough for normal activities. Almost invariably, the patient has been under prolonged tension, or has had overt psychotic manifestations. For months or even years the disease may lurk behind a number of disguises. The following is an incomplete list of preliminary diagnoses made in this series of patients, prior to the establishment of the final diagnosis of lupus erythematosus:

Anemia
Brucellosis
Cerebral vascular accident
Chronic nervous exhaustion
Collagen disease
Dermatitis medicamentosa
Epilepsy
Erythema multiforme
Felty's syndrome
Glomerulonephritis
Hemolytic anemia
Meningitis

Nephrosis	Rheumatoid arthritis
Peripheral neuritis	Scleroderma
Pneumonia	Subacute bacterial endocarditis
Purpura	Syphilis
Raynaud's phenomenon	Trichinosis
Rheumatic fever	Tuberculosis

Perhaps the most common component of the lupus diathesis was the past history suggestive of rheumatic fever, rheumatoid arthritis, glomerulonephritis, or Raynaud's phenomenon.

Once established in a patient, the diagnosis of L. E. or of the L. E. diathesis must never be forgotten. The importance of this lies in the devastating effect of complications on patients with L. E. If another disease develops and the L. E. is not treated, the patient may quickly die. If the complication and the lupus are both treated, the chances of recovery are better. For example, steroidal therapy is usually contraindicated in bacterial pneumonia, but in L. E. patients with bacterial pneumonia it may be necessary to use cortisone, hydrocortisone, or corticotrophin in order to bring about a response to antibiotics. The following case indicates this point.

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CASE REPORT

Mrs. C. D., aged 34 years, was first seen in the Cleveland Clinic on Sept. 23, 1950. Two months earlier, she had noted the onset of fever, joint stiffness, and swelling, associated with malaise, easy fatigability, and an erythematous eruption over the face. A diagnosis of lupus erythematosus was made. The plasma L. E. test was positive. The patient was considered to have subacute systemic lupus erythematosus of a moderate degree, and steroidal therapy was withheld. The patient responded to bed rest, and the eruption disappeared. Several months later, she suddenly developed pneumonia of the right lower lobe and was hospitalized in a local hospital. During six days of penicillin and supportive therapy, her condition had grown progressively worse; death seemed imminent. The lupus diathesis was recalled by the local physician. Cortisone therapy was begun with prompt cessation of symptoms. The patient has remained well for two years on a maintenance program of corticotrophin.

Further experiences have emphasized the need for years of careful watchfulness over patients with the lupus diathesis. No patient is "cured," but only enters remissions. It has been said that "the flame of the burner may go out but the pilot light goes on forever."

SPECIAL MANIFESTATIONS

The clinical manifestations in systemic lupus erythematosus may be generalized or localized, varying with the patient and with the degree of illness. In some instances all organs seem to be involved; in others the disease is localized within one or two systems. The pathologic changes may be extensive but localized within a nonvital organ, such as the skin, lymph nodes, or spleen. In such cases, the patient may not be critically ill. If the disease is localized to the myocardium or to the parenchyma of the kidney, the result may be fatal, although the extent of involvement may be relatively small.

Cutaneous Manifestations.—The clinical variations of L. E. have led to many different classifications. Dermatologists have prepared arrangements of the disease based upon the skin changes but not necessarily excluding systemic involvement. Thus, Kierland and his associates[1,b] in 1940 stated that "lupus erythematosus is a systemic disease," and presented the following classification: (I) Localized, or chronic discoid; (II) Disseminate varieties, (a) generalized discoid or chronic disseminate, (b) subacute disseminate, (c) acute disseminate; (III) Conditions related to lupus erythematosus, (a) Senear-Usher syndrome, (b) Libman-Sacks syndrome. Michelson[1,e] suggested that the term "systemic lupus erythematosus" be limited to those types of the disease which "have no classic picture and often have histories of prolonged rather mild illnesses which gradually become more severe." In the present series, the term "systemic" is used broadly for any clinical picture of lupus erythematosus supported by positive L. E. tests. (Thus, Kierland's group I, mentioned previously, is not reported here unless the localized lesions were associated with clear-cut visceral manifestations.)

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Of the 126 patients in this group, thirty-six had the characteristic erythema of acute disseminated L. E. coincidental with the onset of their illness. In most of these patients the erythema cleared with remissions. In nine instances the erythema changed after therapy into the scarring lesions of discoidal L. E. One of these patients later redeveloped acute lesions and died. Six patients initially had discoidal lesions but later developed systemic disease. Many patients had a history of nondescript eruptions.

Each patient was examined for small patches of scarring permanent alopecia because not infrequently they represented the only residual of discoidal involvement. Temporary diffuse alopecia was not uncommon among the acute cases. Other cutaneous manifestations included early scleroderma, Raynaud's phenomenon, purpura, extensive mucous membrane ulcerations, moniliasis of the mouth, subcutaneous nodules of the scalp, palms, and fingers, and subungual hyperkeratosis.

Although there are some who believe that systemic lupus erythematosus bears no relationship to discoidal lupus erythematosus,[1,d] this study indicates that there is much to suggest a connection between the two conditions.

The importance of establishing a relationship between discoidal and systemic lupus erythematosus lies in the hope for a better understanding of the pathogenesis of these diseases. It is conceivable that an effective treatment for one might also be beneficial for the other.

The findings common to both diseases are: (1) Skin lesions. The distribution of the lesions over the bridge of the nose and cheeks in a butterfly fashion is seen in both the acute and the chronic forms. There is a sharp contrast between the scarring, atrophic, well-demarcated, discoidal lesions and the diffuse erythematous reaction of the disseminated type. However, there are cases in which these types of skin lesions seem to blend into one another. It is rarely possible to see the entire transition in one patient at one time. The change is more apparent when the comparison is made among different patients with distinct degrees of skin lesions ranging from those of the discoidal to those

of the acute disseminated type. At the "Symposium on Lupus Erythematosus" in Minneapolis, in 1950, Michelson presented a group of patients who showed the entire transition of skin lesions from the discoidal through the subacute and acute systemic phases. (2) Histopathology. The pathologic changes of the involved skin are distinctive enough for the dermatopathologist to render an accurate diagnosis 80 to 90 per cent of the time. The changes in the involved skin of discoidal lupus erythematosus vary only by degree from those of the acute form of the disease.[4] Both show atrophy, follicular plugging, liquefaction degeneration, and a banal inflammation. (3) Photosensitivity is common to all types of L. E. (4) The Tiselius electrophoretic pattern may be altered in the same way whether the patient has chronic discoidal or acute disseminated lupus erythematosus. (5) Family tendency. In this series, one patient had systemic lupus erythematosus, and her brother had discoidal L. E. Another patient died from acute systemic lupus erythematosus, and her sister had discoidal lesions. In another family, one patient noted discoidal lesions, but later developed systemic L. E., as did one sister. (6) Conversion of types. Six patients in this group with systemic lupus erythematosus first had discoidal lesions (Fig. 5). Nine others developed chronic lesions when the acute form was brought under control with steroidal therapy (Fig. 4).

A variety of localized or discoidal lupus erythematosus which is frequently confused with acute disseminated L. E. is shown in Fig. 6. Because the microscopic picture in these cases is similar to that of the lymphocytomas of the skin, this variety is not infrequently called "lymphocytic" lupus erythematosus. It occurs almost exclusively in men and usually is first noted after exposure to the sun. The L. E. tests are negative, and in no instance in ten such patients has any systematization occurred. The patients usually respond promptly to bismuth, Atabrine, or chloroquine. Cortisone is contraindicated in this benign type. The term "systemic" is preferred to "disseminated" in the description of visceral manifestations. Jessar, Lamont-Havers, and Ragan[1,f] stated that it is futile to divide the cases of lupus erythematosus into acute and subacute categories, since the disease varies "only in rapidity and severity of onset." While this concept is completely true, the fact remains that both the treatment and prognosis vary with the severity of the disease, so that classification is often useful.

Arthritis and Arthralgias.—Of all the systems involved in lupus erythematosus, the musculoskeletal system is implicated most frequently. Tumulty[5] found that 85 per cent of his patients with lupus erythematosus had joint involvement. Slocumb[6] reported that "in the chronic disseminated form of the disease 20 per cent have joint involvement, in the subacute disseminated type 57 per cent present joint symptoms and in the acute disseminated type 63 per cent have joint disease."

One hundred seven, or 80 per cent, of the patients in this series had joint involvement at some time during their illness. The manifestations varied in severity, type, and duration. Vague aches and pains may have been present around the joints for many years. Not infrequently the tenderness was localized in the supporting tissue or fibrous bands of the extremities. Despite the per-

sistence and severity of the joint distress, there often was nothing detectable on physical examination. The small and large joints of the extremities were most frequently involved. Occasionally the process was limited to a single joint, with every appearance of acute inflammatory arthritis. Rheumatic fever was frequently mimicked, as was rheumatoid arthritis.

Since the arthritis of lupus erythematosus is not specifically characteristic of lupus, other disease entities are frequently diagnosed before the L. E. is recognized. Roentgenograms of the joints are as nonspecific as the clinical picture. Severe crippling rheumatoid arthritis is a rarity, but has occurred in this series before the onset of systemic lupus erythematosus. A similar state occurred in two patients who four years after a remission induced by steroidal therapy, developed disabling rheumatoid arthritis (Fig. 8). These cases present a problem in nosology: Is lupus erythematosus really "malignant" rheumatoid arthritis or is rheumatoid arthritis "benign" lupus erythematosus?

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Fig. 8.—Crippling arthritis developing in patient with acute systemic L. E., four years after continuous steroidal remission.

Regulated aspirin therapy is essential for relief of the moderate forms of fibrositis, arthralgia, and arthritis. With cortisone and corticotrophin the joint improvement is coincidental with the systemic improvement. Later, attacks of tenosynovitis may occur during the remission induced by steroidal therapy. As a rule, this complication does not necessitate an increase in the daily amount of steroidal therapy.

Respiratory Manifestations.—Clinical symptoms of respiratory disease are not uncommon. Dyspnea is a frequent complaint and may be a manifestation of any one of the many respiratory processes of this disease, including bronchopneumonia, pleural and pericardial effusion, congestive failure, and pulmonary edema. Israel[7] found roentgenologic and pathologic evidence of pulmonary or pleural disease in twenty of twenty-two patients having systemic lupus erythematosus.

In summarizing the incidence of complicating diseases in thirty-two patients with systemic lupus erythematosus, Tumulty and Harvey[1,g] noted eight with lobular pneumonia, four with pneumococcic or staphylococcic pneumonia, two with aspiration pneumonia, one with abscess of the lung, and two patients with pulmonary tuberculosis.

Fig. 9.—Subacute L. E., patient bedridden one year with recurrent attacks of pneumonitis, pleurisy with effusion, arthritis. Positive L. E. tests.

Fig. 10.—Same patient as in Fig. 9. Three years after continuous steroid-induced remission (interrupted twice, but followed by acute flare-ups).

The present study reveals that one of the most common and annoying complaints is a chronic pain in the chest wall. This may occur to the right or to the left of the precordium, or along the lateral rib areas. It is unrelated to pleurisy or thickened pleura and presents no auscultatory physical findings. Roentgenograms are normal. The condition is probably a periosteitis or perichondritis; like tenosynovitis it responds better to salicylates and to heat than it does to steroidal therapy.

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Of more critical importance is the necessity for differentiating between pulmonary tuberculosis and specific lupus pneumonitis. On admission one patient had a two-month history of hemoptysis. Roentgenograms of the chest revealed bilateral apical lesions, but repeated gastric aspirations and sputum studies were negative for acid-fast organisms. In a second case, miliary tuberculosis was simulated by a diffuse granular appearance in the lung fields. Since

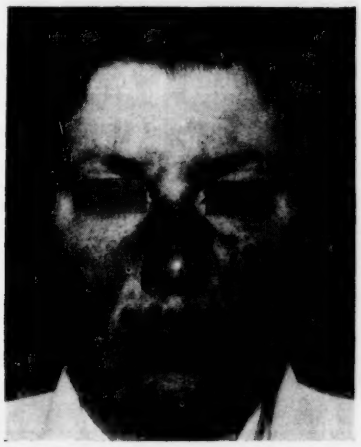

Fig. 11.—Pregnancy occurring during second year of steroid-induced remission. Sixth month. Cortisone dosage during entire pregnancy was 75 to 150 mg. daily, with small doses of ACTH administered weekly. Normal baby delivered (cesarean) at full term, without postnatal adrenal failure.

Fig. 12.—Acute lupus "crisis." Patient in extremis. Massive doses of steroids justified, if needed.

cortisone therapy is capable of disseminating tuberculosis, the importance of diagnostic accuracy in these two cases is obvious. In both, the gravity of the lupus erythematosus was considered to outweigh the risk of disseminating the tuberculosis. After a remission of the lupus erythematosus was induced with

cortisone, the pulmonary changes disappeared in both patients. On the other hand, tuberculous meningitis developed on steroidal therapy in one patient who had no previous evidence of tuberculosis.

Pleurisy and pericarditis with effusion usually responded well to steroidal therapy, and aspiration was not required. In a few instances a cardiac tamponade developed and aspiration was lifesaving. One patient became moribund with a recurrent hemorrhagic pericarditis that did not respond to needle aspiration. Despite the critical condition of the patient, a pericardotomy was performed, which permitted the blood to escape into the pleural cavities. This demonstrated, among other things, the ability of these moribund patients, when properly supported with steroids, to tolerate drastic operative procedures.

Blood Disorders.—Rarely is the blood pattern normal in systemic lupus erythematosus, except perhaps during the early stages of the disease. Instead, the anemia and leukopenia previously mentioned may be accompanied by other abnormalities of the formed elements of the blood and also by alterations in the plasma. Kaposi,[1,a] in his original article in 1872, mentioned a 15-year-old girl who had purpura first, then lupus erythematosus. The modern literature contains many case reports of lupus erythematosus preceded by thrombocytopenic purpura[1,g,8-10] and by hemolytic anemia.[11,12] Splenectomy has been performed with temporary improvement noted in the blood dyscrasia,[13] but without prevention of the onset of the lupus erythematosus.

While the differential count is usually normal in uncomplicated lupus erythematosus, the leukopenia of 2,000 to 3,000 may be accompanied by a striking lymphopenia. The strange, rare phenomenon of 1 per cent lymphocytes in leukopenia makes lupus erythematosus virtually unique, in this respect, among diseases uncomplicated by drug reactions.

The leukopenia may be replaced by a leukocytosis during superimposed infections. In one case, complicated by lobar pneumonia, the leukocytosis reached 33,000 per cubic millimeter, with 92 per cent polymorphonuclear leukocytes. The absence of leukocytosis was useful in differentiating between a complication of lupus and a primary manifestation of the disease. Thus, abdominal pain suggesting either bacterial peritonitis or the serositis of lupus may be presumed to be the latter, if the leukopenia persists.

In severe cases of systemic lupus erythematosus there is usually a complete eosinopenia. As previously mentioned, in a steroid-induced remission the eosinophils may increase from 0 to 30 to 100 per cubic millimeter. Contrariwise, an eosinophilia may occur, but usually indicates an allergic complication.

The plasma proteins in lupus erythematosus are abnormal.[14] In this series almost without exception, the Tiselius electrophoretic pattern usually revealed an elevation of the gamma globulin, but in some cases the alpha and beta globulin fractions were elevated to a higher relative proportion than that of the gamma globulin. Meyer[15] studied the plasma proteins of forty-two patients in this series, and compared the patterns in some over a five-year period. The most constant finding was a hypergammaglobulinemia. Under cortisone therapy the amount of gamma globulin in the blood frequently decreased, but not to within the normal range, except in those with severe renal involvement. Meyer

found the degree of elevation to be of no prognostic significance. He noted that hypoalbuminemia of severe degree was a very poor prognostic sign, especially when the albumin level did not return to normal with treatment. One nephrotic patient had almost an agammaglobulinemia.

In addition, the plasma of a patient having L.E. may contain a number of other elements of interest, indicating the complexity of the disease. The L.E. factor[16] is found within the gamma globulin fraction and is responsible for the induction of the L.E. phenomenon. One of the first detectable preclinical signs of L.E. is the factor that induces biologic false positive serologic tests for syphilis.[22] The heterophile-antibody factor may be present.[1, j] (In one case in the present series the titer rose to 1:22,000.) Conley[8] reported two patients having an abnormal protein in their serum which interfered with the normal clotting mechanism. The Coombs' test factor and cold agglutinins are not infrequently found in the L.E. plasma. Schleicher[17] demonstrated an erythrocyte-aggregation factor in L.E. plasma.

Certain plasma elements may be decreased during active stages of S.L.E., for example, complement[18] and C-reactive protein.[19] The latter may reappear during phases of superadded infection. Periarteritis nodosa, rheumatic fever, and rheumatoid arthritis, unlike S.L.E., are associated with increased C-reactive protein during periods of disease activity.

Renal.—Involvement of the kidneys in the patient with systemic lupus erythematosus is the most serious complication of the disease. Nephritis and glomerulonephritis are the two most common diagnoses, and the prognosis can be considered to vary directly with the percentage of the urea clearance, i.e., the lower the clearance, the poorer the outlook. As mentioned, the urinary sediment can look "like all diseases at once."[2]

Miscellaneous Manifestations.—Space does not permit equal attention to each of the unusual and atypical manifestations of systemic lupus erythematosus. The following group of findings excited special interest among the team of consultants especially interested in lupus erythematosus. In most instances the manifestations were noted in more than one patient.

Cardiovascular: Gallop rhythm and a variety of murmurs were noted on auscultation. In one patient, perhaps with Libman-Sacks vegetations, the heart sounds mimicked a major septal defect. Yet, during a steroid-induced remission, the bizarre, machinery-like murmurs disappeared. The patient is in the third year of a remission, and the heart tones have remained normal. Similar disappearances of the gallop rhythm and of the murmurs were not uncommon.

Gastrointestinal: Often the presenting complaint was nausea, vomiting, or diarrhea. One patient had recurrent febrile episodes, each of which was followed within twenty-four hours by severe, cramping abdominal pain associated with nausea, vomiting, and, later, by diarrhea. Two had superior mesenteric artery occlusion (duodenal ileus) with dilated proximal duodenum. In all three patients the gastrointestinal symptoms disappeared during steroidal remissions. Two patients had hepatitis, one to a severe degree. In both instances, the jaundice was associated with a worsening rather than an improvement of the S.L.E.

Three male patients had peptic ulcers, which remained well controlled despite prolonged cortisone treatment. One patient, also a man, developed a duodenal ulcer during the second week of steroidal therapy. Despite the continuance of the cortisone, the ulcer healed with the usual management. On the other hand, perforation of stomach ulcers occurred in three women who were taking cortisone. None had shown previous signs of stomach distress.

Genitourinary: During the most severe phase of their illness, six patients lost voluntary bladder control, and indwelling catheters were required. Control was restored within the first week of therapy in each case and the phenomenon did not recur. The presence in the urine of bacteria (principally *Escherichia coli*) posed a frequent problem. The significance of this finding in the absence of other evidence of genitourinary disease is as yet to be clarified in these patients. As with other infections in lupus erythematosus, specific antibiotic therapy directed toward organisms found in the urinary tract frequently failed unless supplemented by cortisone.

Pregnancy in S. L. E.: Five patients became pregnant after the diagnosis of systemic lupus erythematosus had been established. Normal infants were born to four. The fifth miscarried during the sixth month of pregnancy, shortly after an attempt was made to discontinue cortisone therapy. Three of the patients conceived, bore, and delivered while on maintenance doses of cortisone which varied from 50 to 150 mg. a day and semiweekly injections of corticotrophin, 10 units each. One patient with mild systemic L.E. had been in remission and had not required cortisone for two years. During the pregnancy no sign of relapse occurred. Two patients developed severe postnatal psychotic episodes, requiring shock therapy. None of the infants developed severe adrenal collapse after delivery, possibly because of the concomitant administration of the corticotrophin to the mothers during their pregnancies. Cesarean section was the preferred form of delivery because it controlled the time and place of delivery. In one patient the eruption increased during pregnancy (Fig. 11).

Surgery in S.L.E.: The following surgical procedures were successfully performed in this series: manipulation of Colles' fracture, appendectomy, treatment of perforated peptic ulcer, treatment of intestinal obstruction, and pericardotomy. Anesthetic requirements were unusually light; preoperative medications included booster doses of cortisone; intravenous hydrocortisone was employed in two cases of postoperative collapse. The main postoperative problems were concerned with proper balance of fluids and electrolytes.

Neurological manifestations: Two patients had peripheral neuritis; the symptoms of one simulated a tumor in the brachial plexus. Seven patients developed herpes zoster. Six were on cortisone therapy at the time of onset of the vesicles, and in one of these six the herpetic eruption was gangrenous and was followed in a few days by fatal lupus relapse. Findings on spinal fluid examinations were variable and nonspecific.

Psychiatric manifestations: A striking feature was the frequently obtained history of stress or entrapment situations before the first clinical evidence of S.L.E. Eleven patients had been under neuropsychiatric care long before

organic manifestations were noted. These conditions included cyclothymic, schizophrenic, epileptic, and a variety of neurotic patterns.

THE L.E. TESTS

The first time the plasma L.E. test was performed at the Cleveland Clinic was in February, 1949. Since then more than 7,000 plasma samples have been tested, including several hundred mailed in to the special hematology laboratory. One hundred thirty-two of the Clinic and seventy-five of the outside tests have been positive. Only six of the 132 routine Clinic tests were considered to be false positive, induced by Apresoline.[20,a,b] Hundreds of normal patients and patients with diseases other than lupus erythematosus have been tested. In any of the strongly positive plasma L.E. tests, where the L.E. phenomenon could be recognized immediately with the low-power magnification, the patient's disease was always compatible with systemic lupus erythematosus. In the weakly positive reactions, when the rosettes and L.E. cells of the L.E. phenomenon were difficult to find, the diagnosis was not infrequently open to question. In general, the specificity of the L.E. tests was confirmed.

PRINCIPLES OF TREATMENT

The medications used in the treatment[21,a-i] of this group of patients having systemic lupus erythematosus can be divided into three groups: those used specifically against the disease, those used against the complications of the disease, and those used as general supportive measures. Several important principles as revealed in this study seem worthy of emphasis.

Specific Medications.—Cortisone and corticotrophin, and later hydrocortisone and fluorohydrocortisone, were the first drugs which could end with any degree of certainty the acute, fulminating phase of systemic lupus erythematosus. Within twenty-four hours, any of these medications may induce a dramatic improvement. Yet, there is an understandable hesitancy in their usage. Once a patient has begun a program of steroidal therapy, a series of checks and balances is necessary to prevent complications inherent within the treatment itself. The control of the patient's disease easily may become complicated by a number of physiologic reactions which in themselves can be serious. This can lead to a hesitating, multimedication treatment program and disastrous confusion.

A mild case of systemic lupus erythematosus should not be treated with small doses of steroids; it is better to use none at all. On the other hand, if the disease state is severe enough to warrant cortisone or one of its derivatives, the therapy should be planned so as to dominate the disease manifestations quickly; according to the individual case, adequate dosages should be prescribed and subsequently, gradually decreased in amount. The cortisone group is never curative in itself, but merely is symptomatic medication. Its administration provides valuable time for factors, as yet unknown, to bring about a more permanent remission. The duration of treatment with cortisone or one of its derivatives which is required to induce that quiescent period varies with each

patient. In this series, about one-half the patients required continuous steroidal therapy. Without it the disease rapidly returned. Some patients required continuous hormonal management for five years. About one-fourth required sporadic or minimal steroidal medication during the maintenance phase, and in one-fourth it was possible to discontinue the drugs entirely. Even in the last group, the disease was not considered to be "cured" but merely in a fairly stable remission.

The successful use of Atabrine and chloroquine in the treatment of the discoidal type of lupus erythematosus prompted their use in some patients having systemic lupus erythematosus. In only one of those latter cases was chloroquine successful in bringing about a remission without the use of adjunctive steroids. In most instances neither Atabrine nor chloroquine was of value in treatment; yet, in some patients there appeared to be a decrease in steroidal requirement while the antimalarials were being administered. More time is necessary to evaluate the full worth of these compounds.

Nitrogen mustard was used in seventeen patients. The first patient was treated with this medication in August, 1950, because of a severe lupus nephrosis. A temporary improvement in the renal involvement occurred, but the patient died several months later. The second patient was treated with nitrogen mustard in September, 1950, and is living and well more than four years later, on no medication of any type. One patient died from agranulocytosis following the use of nitrogen mustard. Responses in others have varied. It appears that this medication may have its main value in the management of renal involvement, for this phase of systemic erythematosus is usually unaffected by the cortisone group of drugs.

Treatment of Complications.—Before steroidal therapy was employed, the treatment of the complications of systemic lupus erythematosus was limited by the inherent characteristic of the L.E. patient to overreact to medications and to surgical procedures. Steroidal treatment controlled that tendency to react, and the treatment of complications such as pneumonia, anemia, heart failure, and dental abscesses was prescribed as in the normal patient. When indicated, antibiotics, digitalis, mercurials, and extensive surgical procedures were employed. Electroshock therapy was used for psychotic episodes in two patients.

Supportive Measures.—Testosterone or depo-testosterone was administered to patients who were on long-term therapy to prevent a negative nitrogen balance and osteoporosis. Antidiabetic and antiulcer programs were successfully instituted when needed. The importance of rest and freedom from worry for a period of several months was emphasized. Children were not permitted to go to school for at least one year after the acute phase, although tutoring at home was permitted and even encouraged in some instances. The home phase of the treatment program now is regarded as of prime importance for the continued success of a maintenance program.

SUMMARY

A survey of the unusual findings in 126 patients having systemic lupus erythematosus (S.L.E.) is presented. From this study, a concept of an "L.E.

diathesis" or a predisposition to the disease is suggested. The importance of accurately performed L.E. tests in confirming the diagnosis in atypical cases is emphasized. Cortisone and corticotrophin therapy in selected cases produced symptomatic remissions, permitting extensive surgical and medical procedures heretofore contraindicated by the inherent capacity of the patient with systemic lupus erythematosus to overreact to medications and surgical procedures.

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Editorials

THE NATURAL HISTORY OF CHRONIC ILLNESS

The lead "Announcement" article in the first issue of this new JOURNAL[1] emphasized, as one of the aims of the Editorial Board, the desirability of studies of the natural history of chronic illness. This is a phase of medicine which demands much further investigative effort.

The etiology of acute infectious diseases, their prevention by public health control measures, their course and prognosis in the absence of antimicrobial therapy, and the extent to which prognosis may be modified by appropriate treatment are now for the most part well understood. The accomplishments in these respects of the past two centuries, beginning with Jenner's first successful vaccination against smallpox in 1769, provide the most brilliant chapters of medical history.

For some chronic diseases, too, great progress has been made as to etiology, prevention, and treatment. A few notable examples are the great chronic infections (tuberculosis, syphilis, leprosy, brucellosis, trypanosomiasis); the deficiency diseases (pernicious anemia, pellagra); metabolic disorders (diabetes mellitus); endocrinologic disturbances (dysthyroidism); and deafness in children.

Many of the important chronic diseases, however, are still mysterious as to etiology, still not preventable by a mass public health approach, still lacking completely specific and curative methods of treatment, and still, because of their insidious beginnings, not adequately documented as to their natural history. Outstanding in this group are certain of the arthritides, hypertension, arteriosclerosis, cancer in its many forms, dermatologic disorders, mental illness, neurological diseases, and others too numerous to mention.

From the point of view of the practicing physician, it is essential to understand the behavior and prognosis of chronic illness *in the absence of definitive treatment*. Without this information, he is unable, critically, to evaluate proposed specific or palliative methods of treatment.

From the public health point of view, it is important to study the etiological background of chronic disease and the multiple factors which contribute to its evolutionary development. Only on the basis of such studies, can there be developed planned and intelligent approaches to control and prevention.

This JOURNAL is fortunate in the opportunity to publish, in its first issues, a group of studies of the natural history of several important chronic diseases: essential hypertension[2]; peptic ulcer[3]; systemic lupus erythematosus[4-6]; syphilis[7]; and postnecrotic cirrhosis of the liver.[8] Each of these deserves brief editorial comment.

Perera[2] deals with the progress of events in a series of patients with essential hypertension, none of whom was treated by any one of the three present-day

methods of "specific" treatment, that is, sympathectomy, sodium restriction, or chemotherapy. His data provide, therefore, a base-line estimate of the incidence of complications and the expected duration of life in a population group of stated race, age, sex, and socioeconomic distribution. The alterations in the natural evolution of hypertension, to be achieved by present or future therapeutic efforts, can be evaluated against these and similar base-line data. The medical literature is singularly devoid of studies comparable to those of Perera. Indeed, the only one which comes to mind is that of Bechgaard.[9]

Flood[3] presents a somewhat discouraging picture of the results of the conservative (medical) management of peptic ulcer. He makes it abundantly clear that in his material, at least, medical therapy is usually episodic, in the sense of patient failure to continue even moderate dietary restrictions for long after original symptomatic relief is obtained. In a sense, therefore, his data, too, are a contribution to the natural history of peptic ulcer; and can serve as a base line for evaluation of more specific medical therapy with anticholinergic drugs, or surgical procedures.

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The biostatistical methodology of determination of prognosis in chronic disease is discussed by Merrell and Shulman,[4] using systemic lupus erythematosus as an example. This article is of great importance to physicians, to many of whom the correct statistical methods of dealing with medical data are an impenetrable mathematical mystery. Merrell and Shulman discuss the factors of selection of cases, conscious or unconscious on the part of the investigator, the essentiality of explicit definition and description of the material, and the choice of sound analytic methods. In chronic disease, especially, vital issues are the point of entry of the patient into the study (shall this be the date of correct diagnosis? or shall it be the date of the first symptom of the disorder, so often impossible to recognize because of insidiousness and vagueness?); the variable length of follow-up, based on different calendar times of entry and loss from observation; and the end point (in chronic illness, this is presumably death). They conclude, as have most biostatisticians but too few physicians, that the life-table method of analysis represents the best approach, the use of which by students of chronic disease will eventually permit the creation of a literature in which the results of one investigator will bear comparison with those of another.

Merrell and Shulman apply this method to a study of prognosis in systemic lupus erythematosus, utilizing 99 cases, of which 87 were verified, by the L.E. cell phenomenon, biopsy, or autopsy (or a combination thereof) and 12 were "clinically apparent" but unconfirmed. Their data indicate that the prognosis of S.L.E. is considerably better as to expected duration of life than the literature heretofore available would suggest.

In somewhat different fashion, Haserick[5] reports long-term observation of 128 patients with verified S.L.E. Unlike Merrell and Shulman, he devotes considerable attention to steroid hormone therapy, which, he is convinced, significantly prolongs life in many patients.

Moore and Lutz[6] approach the natural history of S.L.E. from an entirely different point of view. They start, not with verified S.L.E., but instead work with a group of patients who are for the most part, at entry into the study, in

supposed health. The identifying point of entry is the routine discovery of a positive serologic test for syphilis (with standard lipoid antigens), demonstrated by appropriate techniques to be biologic false positive. The long-term follow-up of such patients, averaging presently about six years in their series, indicates that an important proportion of them slowly develop a chronic episodic illness with the clinical characteristics of S.L.E., and in 10 of 148 cases, this diagnosis has been verified.

Peters and his associates[7] present a portion of a long-term study of the natural history of untreated syphilitic infection. Information of this sort is obtainable only with extraordinary difficulty. Since syphilis was first recognized in Europe in 1493, the inclination of physicians has been to treat the infection, when recognized, with something: guaiac, mercury, arsenic, bismuth, and now antibiotics. To find and follow a large series of patients from whom treatment was deliberately or inadvertently withheld is nearly impossible. The only other approach to this problem is in the remarkable study of Bruusgaard in Oslo,[10] now under resurvey twenty-five years later by Gjestland. In a later issue this JOURNAL will have the opportunity of publishing a detailed summary of the 1951-1954 Oslo study of the course of syphilis in a large number of patients from whom treatment of any sort was deliberately withheld (between the years 1891-1910), and who were then followed for ten to sixty or more years.

Finally, Ratnoff and Patek[8] present a survey of the natural history of postnecrotic cirrhosis of the liver as exemplified by 1 living patient and 44 fatal cases. This study is of especial interest since it permits a detailed comparison of the course of this relatively uncommon type of liver disease with a large series of patients with Laennec's cirrhosis studied by the same authors.

None of the papers cited herein offers detailed therapeutic advice; indeed, in most cases none at all. But their data serve as measuring rods for comparison with the material of other authors who advocate one or another therapeutic regimen, and are hence of inestimable value. This JOURNAL will endeavor to publish other studies of the natural history of chronic illness.

J. E. MOORE

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GOUT

The dysfunction of uric acid metabolism which results in articular distress and is identified as the clinical entity, gout, is one of the best examples of a chronic disease in that the disturbance may be present throughout the greater portion of the lifespan. Certainly it persists throughout the natural life of the afflicted once it has been recognized. Furthermore, as a chronic disturbance, in contrast to an acute disease, death in gout is not a sequel of the primary dysfunction, per se. When death occurs prematurely in patients with gout it is because of a complication such as renal insufficiency, or from some unrelated and incidental process. Few maladies in clinical medicine possess as long a natural history as does gout.

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The probable incidence of gout in the United States is not accepted by all contemporary physicians. There are some who seriously doubt the existence of the disease. I quote from Dr. William Brady, the medical columnist: "It is my belief that there is no such disease or ailment as gout, if gout means an accumulation or deposit in joints or other tissues of uric acid which accounts for the pain.

"I dispute the medical myth of 'gout' and I base my denial of the entity on these facts:

"1. Precise measurement of the amount of uric acid in the blood fails to show a consistent increase over the normal or ordinary amount in cases of alleged 'gout.'

"2. A good many individuals have deposits or accumulations of monosodium urate (tophi) in their tissues although they have not and never have had any ailment that could answer the classical description of 'gout.' "

The disproportionate sex ratio, approximately 20:1 in favor of the male, is recognized by the believers. The relatively high familial incidence is less widely accepted. In our clinic, where special attention has been given to the study of gout, familial incidence is discovered in more than 75 per cent of the cases. This datum may not be revealed upon casual questioning at the initial examination. During regular subsequent examinations, however, an uncle or a grandfather may be discovered to have suffered from acute arthritis of the extremities or a closer relative may develop clinical symptoms highly suggestive of the dyscrasia. An example may illustrate this point.

In 1940, when I was practicing in Massachusetts, I was requested to help a 45-year-old man who had had acute attacks of gouty arthritis for more than a decade. His physician was convinced of the diagnosis and commented that this represented an instance of spontaneous development in a family without any stigma of the disease. After the immediate problem of management of the acute attack had been resolved, inquiry concerning the other members of the family was made. A 5-year-old son was the only male descendant, and I did not press for a serum uric acid determination at that time. The only living male ancestor was the father, aged 78, a vegetarian by preference for many years. He had

chosen a low-protein diet as an engineer in the diamond mines in South Africa in the years before World War I, when preservation of meat in the mining settlements left much to be desired. When questioned, this 78-year-old specimen of excellent health denied any symptoms in his past suggestive of acute gout. The concentration of uric acid in the serum, however, which he permitted me to take, revealed a value that was in the same range as his son's, the patient. It is interesting to note that three years later, at the age of 81, the vegetarian suffered his first attack of gouty arthritis. Two years later he had a second attack.

There are several similar instances in our records of brothers or uncles of patients who have developed an initial attack of gouty arthritis subsequent to the examination of the patient. These have been reported to us because of our specific charge to them to take note of such medical items. The incidence of an elevated uric acid in the serum of nonaffected relatives is appreciable. In the largest series that have been reported, from 20 to 25 per cent have shown an increased concentration of uric acid in the serum without other justification for a diagnosis of gouty arthritis. What is the incidence of acute gout subsequently in this "nonaffected" group or how long does the uric acid remain elevated in the serum before the onset of acute gout may be anticipated? The diamond vegetarian discussed previously had a known interval of three years only. On the other hand, we have several nonaffected relatives in our series who have had an elevated serum uric acid for more than fifteen years without any clinical evidence of arthritis. Another illustration should help.

In 1948 I was requested to provide terminal medical care for a patient in advanced renal insufficiency who had had acute attacks of gouty arthritis for almost two decades. Following the initial shock of his demise, complete cooperation with his three brothers, two sons, and two nephews furnished revealing data. Two of the three brothers, both sons, and both nephews had an elevated uric acid. Roentgenograms of the hands and feet in each instance were negative, however, and there was no past history of arthritis in the group. These males have been seen at intervals of eighteen or twenty-four months, and the increased concentration has been confirmed. One of the brothers, who was 50 when he was first seen, had uric acid concentrations of 8.6, 7.4, and 7.0 mg., respectively, between 1948 and 1953. In the fall of 1954, six years after the initial determination, his family physician reported the sudden onset of acute distress in the great toe. The clinical diagnosis of acute gout was confirmed, and the concentration of uric acid in the serum was 8.7 mg. The other "nonaffected" relatives persist in showing an elevated concentration of serum uric acid without any symptoms of articular disease.

These isolated observations lend support to my conviction that the increased concentration of uric acid in the body is a chronic process and persists throughout the greater portion of life as an inborn error of metabolism. The development of uric acid calculi, renal insufficiency from urate deposition in the kidney, or acute arthritis is unpredictable and subject to great variation.

Uric acid is a naturally occurring substance in the healthy as well as the sick. It is one of the end products of purine metabolism and is intimately related to tissue catabolism. As a degradation product of purines, this substance may arise

from exogenous or endogenous sources. There is yet a third possibility for the formation of uric acid, that is, synthesis by the body from some of the simpler carbon and nitrogen compounds. Each of these three pathways may contribute to the formation of uric acid in the human being.

Significant advance in the understanding of uric acid metabolism with the use of C^{13}-, C^{14}-, and N^{15}-labeled compounds have been made during the past decade. These investigations have demonstrated the multiplicity of sources of constituents of the uric acid molecule as well as the multiplicity of pathways that the carbon and nitrogen and probably also the oxygen and hydrogen components travel in order to reach the end product. Equally important in recent investigations has been the administration to gouty and nongouty subjects of uric acid labeled with N^{15}. The data derived from the studies of labeled uric acid have resulted in the concepts of metabolic pool and turnover rate.

The ingestion of purine foodstuffs is followed by an increased excretion of uric acid in the urine. The nucleoproteins are broken down in the intestinal tract by a comprehensive enzyme system to adenine and guanine as well as to other substances which are oxidized to uric acid. Further breakdown to allantoin does not occur in human beings as it does in animals. Uricase, an enzyme either absent or present in minimal amounts in the human being, catalyzes this breakdown in animals. The formation of uric acid from endogenous nucleic acid is of considerable magnitude. At least 300 mg. of endogenous urate may be excreted daily on a purine-free diet. It has been shown recently by the labeling technique that nonpurine substances may be incorporated into guanine, adenine, and tissue nucleic acids, portions of which may be incorporated subsequently into the uric acid molecule. Various workers utilizing various species have shown that carbon dioxide, formate, lactate, glycine, serine, and threonine may contribute to the formation of uric acid.

A related but quite different approach to the understanding of the uric acid disturbance in gouty subjects has been the use of labeled uric acid in the determination of the metabolic pool (miscible pool) and turnover rate. Uric acid may be synthesized with isotopic N^{15} in the one and three positions of the molecule. As small a quantity as 25 mg. of the purified labeled uric acid may be injected intravenously for a satisfactory determination. Complete urine samples are collected for approximately one week and are partitioned into four- or six-hour periods. The uric acid is isolated from the urine, converted to ammonia, and subsequently broken down into nitrogen. The determination of the ratio of N^{15} (heavy nitrogen) to N^{14} (naturally occurring nitrogen) is made in a mass spectrometer. The metabolic pool has been determined in nongouty and gouty subjects in several laboratories. The agreement of data is satisfactory. Certain assumptions have been commonly made to derive the values for metabolic pool and turnover rate. It is presumed that all of the uric acid in the body which participates in the metabolic pool is freely diffusible and at the same concentration throughout the body. It is assumed further that the injected labeled uric acid mixes completely and immediately with all of the uric acid in the pool and that the molecules of isotopic uric acid are indistinguishable from the naturally

occurring ones in so far as metabolic processes including excretion are concerned. There are additional assumptions, which need not be recounted in this communication.

The amount of uric acid in the metabolic pool of a nongouty subject averages slightly more than 1,000 mg. The turnover rate is approximately 0.7 pool per day. The patient with gout has a metabolic pool that is considerably above that for normals and the turnover rate, significantly less, irrespective of the presence of demonstrable subcutaneous or osseous tophi. In our laboratory the metabolic pool of most gouty subjects, prior to the administration of agents which influence this value, varies from 2,000 to 5,000 mg. Considerably higher values have been reported from other laboratories. The turnover rate of the gouty usually is 0.5 pool per day or less. The determination of the miscible pool and turnover rate supports the presumption that there is an increased formation of uric acid in the gouty subject and offers an intriguing experimental tool for the study of the effects of antigout agents.

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An increased metabolism of purine bodies and an increase of the urate content of body fluids need be but slight to account quantitatively for the increased metabolic pool of uric acid. In patients with chronic leukemia, an increased production of urates may lead to deposition in the joints and acute articular symptoms indistinguishable from those of gout. Direct support for overproduction of urate has been reported recently utilizing glycine labeled with N^{15}. When this substance is injected intravenously, some gouty subjects show a higher concentration of uric acid tagged with N^{15} in the urine. Benedict and associates[12] have assumed that the increased formation of urate is at the expense of urea and proceeds through a more direct pathway. Not all patients with gout, in the small number studied, have shown an increased formation of uric acid from glycine. This raises the question as to whether or not there is more than one principle metabolic defect responsible for the clinical malady. None of the nongouty controls has shown an increased formation. The laborious technique of the isotope studies in human beings precludes the accumulation of a large number of subjects to confirm or reject this presumption.

Other evidence in support of an increased formation of uric acid, an integral aspect of the pathogenesis of the disturbanace, has been available for several decades. Almost from the beginning of modern clinical biochemistry, an occasional patient with gout was observed to excrete more uric acid than a control subject on a constant diet. Folin[4] was one of the first to make this observation. This was confirmed several years ago in our laboratory[9] and more recently by Friedman and Byers[11] as well as by Gutman and Yü.[10]

If overproduction of urate is not responsible for the metabolic dyscrasia, one may inquire regarding decreased destruction of uric acid by the body or impaired excretion of the kidneys. There are no strong proponents for the impaired destruction hypothesis, and the impaired excretion explanation is increasingly less popular. Normal exchange of urate by the kidney in gouty subjects usually is the rule in mild or moderately afflicted cases. Those who suffer maximally from the malady may have extensive renal changes which may alter the exchange of

urate. Such changes appear many years after the initial attack of acute arthritis and are believed to follow rather than to precede the disturbance of uric acid metabolism.

The diagnosis of acute gouty arthritis may be made upon the clinical evidence and further confirmed by laboratory studies. A past history of a urate stone, a family history of gout, or the detection of a transient albuminuria may point the way. The greatest help in diagnosis, however, is obtained from the clinical characteristics of the acute attack. The sudden onset of acute distress in one of the peripheral joints of the hands or the feet of a male points to one diagnosis only. In the early years of the disease, x-ray changes are not to be expected, and tell-tale subcutaneous tophi will not yet have appeared. The response to colchicine when given orally or intravenously may be extremely helpful. Colchicine is specific for acute gouty arthritis and has no significant antiarthritic effect in other types of joint disease. Without exception, the other antirheumatic agents that may be given for acute arthritis, such as salicylates, phenylbutazone, and the steroids, are endowed with no diagnostic implications. Relief may follow administration of any of these in gouty arthritis as well as in nongouty arthritis.

The concentration of uric acid in the serum may be extremely helpful in diagnosis. Serum or plasma rather than whole blood should be used. The patient should be taking no antirheumatic drug within a forty-eight-hour period of the serum concentration determination. Each of the nonspecific agents mentioned may have a uricosuric action and complicate the interpretation of the laboratory result. Failure to appreciate this possibility has led to considerable skepticism regarding the value of the uric acid determination. In our clinic the patient with gout has an increased concentration of uric acid in the serum above 6 mg., irrespective of the stage of the disease and irrespective of the time in relation to an acute attack. The only agents that modify the concentration are those that lead to an increased excretion of uric acid by the body, that is, the antigout agents other than colchicine. Colchicine has no demonstrable effect upon uric acid metabolism.

The prognosis in this chronic disease is excellent. With the earlier and increased recognition of the disease, the proportion of those severely afflicted has decreased significantly. In the series of patients that I have been following during the past decade, not more than 2 or 3 per cent have died or will die prematurely of the disease. More than 90 per cent of those afflicted suffer surprisingly little and are able to lead normal lives. We see an occasional patient who represents an exception to this generalization. Strangely enough the two most unhappy patients with gout whom I can recall are physicians who refuse to follow medical advice. One became a heroin addict because he preferred this agent to colchicine in the treatment of his acute attacks. The other physician preferred one week or ten days of incapacity three or four times a year because he could not be "bothered" with one or two colchicine tablets each day. During the past couple of years he has been more cooperative and takes benemid and colchicine several times each week. Over and above these disgraceful examples are the vast majority of gouty patients, who are cooperative and delighted to

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follow a relatively simple regimen in return for the opportunity to live a normal life and pursue a gainful occupation. This optimistic prognosis has been amply enhanced since 1950, when benemid was introduced. Even before 1950 the agents that were available contributed greatly to the treatment and prevention of acute arthritis in those moderately or severely affected. In others the disease appeared in a low degree and did not progress in a detectable manner decade by decade. Probably in this category it made little difference what dietary or therapeutic regimen was recommended beyond that of sensible living.

The management of acute and chronic gout is probably more satisfactory than that of any other chronic joint disturbance. Gout is a gratifying disease to treat since it exalts the ego of the physician. There is nothing more gratifying than to find some poor soul in excrutiating pain, appetite gone, having chills and fever, unable to sleep, and generally miserable, and have him undergo a remarkable transformation within a period of twelve to sixteen hours and be back on the job within a few days. This may be accomplished with oral or intravenous colchicine in a high percentage of instances, with phenylbutazone in a majority of instances, and with large amounts of cortisone, hydrocortisone, or corticotropin in a few instances. My preference for the several agents is in this order. If the acute attack has been present, untreated or poorly treated for one day or longer, recovery may be less dramatic. If the joint distress does not respond to full doses of colchicine, the diagnosis should be questioned or some complication should be sought. During convalescence from acute gouty arthritis, early ambulation is to be encouraged. There are no other specific measures to be recommended for the treatment of the acute episode.

The management of the intercritical periods, which should encompass most of the time for all patients with gout, comprises a few drugs and a few prohibitions, in short, a simple regimen. A high fluid intake is to be stressed. This aids in the elimination of uric acid from the body, a particularly important feature when benemid is prescribed. Weight reduction, if indicated, should be insisted upon. Substances high in purines, such as liver, kidney, and sweetbreads, should be avoided. This usually entails no hardship. Alcohol in moderation and red meat are permitted for most patients. The amount of physical activity should be determined by factors other than the presence of gout.

It is believed that there are only two drugs that should be used regularly in the intercritical period. These are colchicine, one of the oldest specific drugs in the pharmacopoeia, and benemid, one of the newest. I prescribe for patients moderately afflicted with gout, 1 or 2 colchicine tablets daily throughout the year. Those severely afflicted take 2 or 3 tablets daily. Gastrointestinal tolerance is the determining factor for these patients. Chronic tolerance does not develop under any circumstances, and acute toxicity from colchicine is confined to gastrointestinal irritability. The patients mildly afflicted may take colchicine either daily or only occasionally. Colchicine significantly reduces the incidence of acute attacks regardless of the severity of the disease.

The introduction of benemid early in 1950 filled a void in the therapeutic armamentarium that had been recognized for more than a century. Uricosuric agents were available before benemid, but no single agent prior to 1950 was a

practical answer to the request for a substance that would achieve satisfactory uricosuria in relatively small amounts and be endowed with negligible toxicity. Approximately 1 Gm. of benemid will result in satisfactory uricosuria in most patients if taken daily. A decrease in the concentration of uric acid in the serum of from 25 to 35 per cent with a concomitant increase in excretion in the urine follows. The concentration of uric acid in the serum is restored to normal or near normal and persists as long as the drug is taken. During the five-year period that this preparation has been available the favorable results have predominated; the untoward results have been minimal. Benemid may slightly increase the tendency to form stones. However, it should not be forgotten that approximately 15 per cent of all patients with gout have a history of calculi independent of administration or uricosuric agents. Gastrointestinal irritability appears in some but usually can be corrected by sympathetic handling. An occasional person will develop a skin rash. Most patients tolerate the drug in an excellent fashion.

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The persistent decrease in the concentration of uric acid in the serum that follows benemid administration is associated with a decrease in the incidence of acute attacks. This effect augments the prophylactic action of colchicine. The combination is responsible for the present satisfactory status of the management of the disease. At this stage of our clinical investigation of the value of benemid it is recommended that those severely afflicted with gout remain on benemid and colchicine for an indefinite period. Those mildly afflicted are permitted considerable freedom. One patient was on benemid and colchicine for approximately three years and, having suffered no acute attacks, was permitted significant modification of the therapeutic regimen. During the past year he has taken a few benemid and a few colchicine tablets each month and has remained clinically free. It is anticipated that in this category of patients, similar leniency will probably be in order. Since the escape from benemid is rapid and return to the gouty range follows within twenty-four or thirty-six hours after ingestion of the last benemid tablet, I do not believe that a patient should remain off benemid for a long period of time, even though he may be clinically free from acute attacks. Since gout is a chronic disease, the disturbance of uric acid metabolism persists as long as the patient lives. The threat of an acute attack remains with the increased concentration of urates in body fluids.

Each chronic disease should be attacked persistently. It is fortunate that gout is subdued so long as the offensive is maintained.

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HOME CARE OF CHRONIC ILLNESS

CHANGING ILLNESS REQUIRES CHANGING PHILOSOPHY AND FACILITIES

In 1950 it was estimated that about 5.3 million Americans were afflicted with a chronic disability or impairment of sufficient severity to incapacitate them for more than three months. It may seem curious to state that this startling increase in the burden of chronic illness is due to progress, since we all associate progress with the good and sweet things of life. Nevertheless, it is true in the health field, as in many other areas, that whatever we get we pay for. The conquest of bacterial illnesses and other brilliant medical and public health achievements of the last one-half century have given more of us longer life; but we have not defeated death—only postponed it, and disease has not been banis[l]ed—only changed.

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During the heyday of acute illness, the general hospital was the ideal place not only for the care of the serious acute illness, but also as the training place for physicians and other health personnel. Most physicians have been so thoroughly exposed to the virtues of in-hospital patient care that it seems to them almost indecent to think of good medical care in any other setting.

It is one thing, however, to provide institutional care for serious medical problems which take only days or a few weeks to come to a clear-cut decision. It is quite another to use hospital beds for people who, by the millions, will be sick with illnesses whose duration is measured not in days, but in months or years. Even our rich community does not have the financial and personnel resources necessary to meet the major portion of the needs of the chronically sick by the erection and maintenance of hospital facilities. We are therefore forced by changing conditions of illness to change the weapons and the places that we use to meet the needs of the sick. In the care of the long-term sick, hospitals must for the most part confine themselves to definitive diagnosis and, where it is possible, specific therapy. The great bulk of the care of patients with long-term illness, now and in the foreseeable future, must be carried on either in the home or some suitable substitute for it. It is fortunate that the necessity for home care for the chronically sick turns out to have considerable virtue.

WHAT ARE THE CHARACTERISTICS OF CHRONIC DISEASE?

To develop proper facilities and services to meet the needs of this ever-increasing burden of the chronically ill, it is essential that we understand the character of the problem so that the solution will be appropriate to the needs. The outstanding characteristic of chronic disease is its length, and this in fact creates many of the problems. In serious acute illness the decision is quick;

hospital stay short; and the resources of the family, both financially and emotionally, are usually adequate, since rapid return of the patient to previous good health, job, and family is anticipated. Quite the reverse is true in chronic disease. The period of illness is long; most often there is no clear and complete recovery; frequently some handicap prevents return to the previous occupation.

Chronic illness not only presents a threat to health and life but also creates for the patient and his family serious social, emotional, and economic disorders. Chronic disease and poverty go hand in hand, for few families can withstand the impact of expensive medical care and hospitalization for long periods of time. Of even greater significance is the dislocation which chronic disease creates in family situations. Man is a physiologic whole, and one organ or one symptom cannot be considered to the exclusion of the others. It is just as vital for us to recognize that man, for all his seeming independence, is not alone but is inextricably a part of a family and of society. When a man of 50 with a wife, children, and a job suddenly is told that he has severe heart disease, he finds the whole structure he has built through fifty years about to crumble. His role as leader and head of the family is gone. Where he was the provider, he now must be provided for. His relationship with society generally has been seriously altered, since one of the marks of the whole man is his ability to go out to work, to hold a job, and to provide for his family. Many of us have seen patients with serious illness who suffer a greater lack of well-being because of the disordered situation which the illness produced in their families, than from the illness itself.

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While the hospital has great virtues for patients when they are desperately in need of its technical facilities and professional skills, it is obvious that the hospital is not the natural habitat of human beings, and that the glamor which surrounds the hospital for those who work in it does not necessarily extend to those who are cared for in it. Institutional living imposes necessary restrictions upon patients so that the organization may function adequately; but where the benefits of hospital care are not great, the restrictions and the discipline become oppressive. Since care for the chronically sick must extend over long periods of time, it is important that the ingredients of warmth, concern, and affection be maintained. The characteristics of chronic illness and its concomitant aberrations therefore require attention not only to medical and nursing problems, but to emotional and psychiatric components. These facets can be well handled by a basic team of doctor, nurse, and social worker. If it is possible within the framework of the home to provide the necessary medical, nursing, and social services essential to meet the total needs of the patient and his family, then the coldness and rigidity of the hospital can with profit be exchanged for the warmth and flexibility of the home.

HOME CARE EXPERIENCE

That home care is not only theoretically but actually feasible is evident from the programs springing up throughout the country. At the University of Syracuse, in 1941, a program entitled "Medical Care of the Discharged Hospital Patient"[1] indicated that important medical values attached to caring for patients

in the home after they left the hospital. This resulted in fewer and shorter subsequent hospital admissions. The estimated financial savings far outweighed the cost of the program. At Montefiore Hospital, in 1947,[2] a comprehensive program of home care for the chronically sick was begun which demonstrated the effectiveness of the team in meeting the needs of the chronically sick in the home environment. It showed that a significant portion of the population of Montefiore Hospital which had hitherto required institutional care could, under this broad program, be adequately managed in the home. The range of services provided included not only the physician, nurse, and social services, but also laboratory, housekeeping, occupational therapy, physical therapy services, drugs, medications, hospital equipment, and prosthetic appliances. While the social and professional values of the program are the most important, it is comforting that care is significantly less expensive in the home than in the hospital. Two-thirds of the financial burden of the hospital cost is payroll; and much of the care which people require in the home can be and is given by members of the family with no great sacrifice to themselves and with great benefit to the patient and the community.

There are many programs with different administrative arrangements and under a variety of auspices.[4] Some of the significant ones include the program at the Massachusetts Memorial Hospital under the auspices of the Boston University School of Medicine; and the home care program in Richmond, Virginia, under the auspices of the Department of Health and the Medical College of Virginia. The Boston Dispensary, one of the pioneers, has conducted a home care program since 1796. Under the Department of Hospitals of the City of New York there are home care programs in thirteen city hospitals with a daily patient census of approximately 2,000.

THE FUTURE

It seems inevitable that home care will play a continually expanding role in the managment of long-term illness not only because we cannot afford to provide prolonged institutionalization, but also because, for properly selected patients, home care represents the best kind of care, since it allows the patient to live with his family in a personalized, warm, and free atmosphere.

For the future development and broader use of home care it is significant that such organized programs have been developed in conjunction with or by some medical schools as a teaching device. Students are introduced into the home, where people can be seen in a natural setting and where the impact of disease on the family can be understood not as social work phraseology but as a living thing.[4]

Home care is not a panacea for all the chronically sick. Patients must be carefully evaluated to determine their medical and social suitability for it. Where the ties between patient and family are close and where the basic team of the doctor, nurse, and social worker stand ready to provide service, then home care is an effective, positive, preferred method of meeting the multiple needs of the chronically sick. The same reasons which make such programs desirable for the care of the chronically sick also make them a fruitful area for professional education for students and physicians.

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Book Reviews

SPATIAL VECTORCARDIOGRAPHY. By George E. Burch, J. A. Abildskov, and James A. Cronvich. Pp. 173, with 121 illustrations. Philadelphia, 1953, Lea & Febiger.

This volume reproduces an exhibit which was displayed at a meeting of the American Medical Association in 1952, presenting the basic concepts of spatial vectorcardiography and the results of the authors' clinical investigations in this subject. The resulting style has the virtues of being concise and of being directed at a general medical audience. The authors' conclusions about technique and clinical applications are clearly stated, and the reasons for their conclusions enumerated in order. Their findings in cases of myocardial infarction and other abnormalities are summarized under the refreshing heading "Impressions" at the end of each chapter. Specialists will disagree in detail with some of the conclusions, but will at the same time appreciate the authors' unequivocal statement of their opinion.

To the question, "What use has vectorcardiography in clinical medicine today?" the Tulane group gives the answer, "We are not sure yet." On the basis of the evidence available, this is the only reasonable answer possible. It seems unlikely that cathode-ray spatial vectorcardiography will ever replace conventional scalar electrocardiography, partly for technical reasons, and partly because the two methods are simply different ways of measuring the same phenomena. The recording of vector loops may prove to be a useful supplementary method in some cases, but more information is needed before agreement can be reached even on this point. Dr. Burch and his colleagues emphasize that "Vectorcardiography is not yet suitable for general clinical application. It is still in the experimental stage, its practical clinical applications not yet having been demonstrated," but ". . . practical applications may be reasonably expected in the near future."

William R. Milnor

HEART DISEASE. By Paul Dudley White, M.D. Ed. 4. Pp. 1000, with 168 figures; indexed. New York, 1954, The Macmillan Company. Price $12.00.

The fourth edition of this classic book meets high expectations. Few medical authors can combine in a textbook scientific accuracy, felicity of expression, thoroughness, and completeness of content as well as White. The general plan of the third edition is followed, although the format is improved greatly.

The first part of the book deals with cardiovascular examination, symptoms, and signs. Roentgenology of the heart, ballistocardiography, and electrocardiography are treated briefly but adequately. Perhaps the short discussion on vectorcardiography and the ventricular gradient could have been omitted.

The second section deals with the significance, prevalence, causes, and types of heart disease. The chapter on congenital heart disease is well conceived, and the colored diagrams borrowed from Taussig's book are a distinct aid to the understanding of the abnormal circulation. The whole section is written in the light of recent advances in diagnosis and treatment. Rheumatic heart disease, bacterial endocarditis, cardiovascular syphilis, and the relationship of other infections and infestations to the heart receive appropriate consideration. Hypertensive heart disease is described as the most common and important of all types of heart disease. Between forty and fifty drugs are mentioned as having been used in the treatment of hypertension. Obviously the newer drugs could not be discussed in this edition published in 1951. However, White has great enthusiasm for Smithwick's operation of sympathectomy.

Coronary heart disease logically includes in one chapter angina pectoris, coronary thrombosis, and myocardial infarction. A notable omission in this chapter concerns the important and debatable factors that precipitate acute coronary artery occlusion.

The relationship of heart disease to pregnancy, anesthesia, surgical operations, alcohol, and smoking receives adequate attention.

Part three deals with structural cardiovascular abnormalities. This includes, among others, two important chapters on endocardial and valvular disease, and on pericardial disease, both acute and chronic.

The final part is concerned with disorders of cardiovascular function, including congestive heart failure, and the numerous arrhythmias. This is complete and up to date, with excellent illustrations.

The whole book is arranged beautifully with interesting historical references and a complete bibliography.

This reviewer has never read a medical book with such genuine pleasure.

Neil Feeney

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CONGENITAL SYPHILIS. By David Nabarro. Pp. 454; cloth. London, 1954, Edward Arnold & Co. Price $10.00.

To read this book is to savor of old wine; and like old wine, it is for the connoisseur. Also, like old wine, it is somewhat musty, and contains an inordinate quantity of dregs. It is a book for the physician to read by the firelight of a winter's evening, and cannot be recommended to the busy student or practitioner avid for accurate and practical knowledge.

The author was Medical Officer in charge of the Venereal Diseases Clinic at the Hospital for Sick Children, Great Ormond Street, London, from its inception in 1917 until its closure in 1939. The book is largely based upon the nearly 900 cases of congenital syphilis seen during the twenty-three years of its existence. It is a historical record of the disease as seen in Britain in the prepenicillin era.

The keynote of the volume is set by an excellent illustrated chapter on historical aspects. A mighty march of masters, from Paracelsus to Parran, passes in figured review. There follows an adequate discussion of the incidence of congenital syphilis with proper emphasis upon its decline as well as upon the relative lack of reliability of published rates.

The ensuing chapter on the transmission of the disease is truly anachronistic. The author exhibits a curiously persistent belief in the nineteenth century theory of paternal transmission. "It is possible for the first infected child to be an instance of paternal transmission, and that the mother is infected by that child ('choc en retour')." The metaphysics of maternal germ transmission have been disinterred. "It is possible, too, that the genes of the germ-cells may be so affected by resting or attenuated form of the parasite (or by an alleged syphilotoxin) that a true hereditary effect upon the offspring may result."

There follows a brief discussion of the general pathology of the disease and of serologic and spinal fluid tests. The important problem of biologic false positive reactors is disposed of in less than a single page of text.

The detailed consideration of the symptomatology of congenital syphilis, with numerous illustrative cases from the author's clinic, is, on the whole, excellent. Particularly to be commended are the discussions, with photographs and radiographs, of cutaneous manifestations, dental stigmas, and involvement of the bones and joints. A persistent belief in the thoroughly discredited Warthin lesion and in the ubiquity of the *Treponema pallidum* mars the discussion of cardiovascular involvement in congenital syphilis. "I would go further and suggest that some of the attacks of so-called rheumatic carditis and even chorea may be manifestations of treponemal activity which would benefit by treatment on antisyphilitic lines even though the W. R. be negative."

Consideration of central nervous system involvement is fundamentally sound but not entirely adequate. Discussion of pathologic anatomy is sketchy. The clinical picture of juvenile paresis might well have been more vividly painted, and concerning its treatment the author states.

". . . in my view treatment should not be relaxed until blood and C. S. F. are both W. R.-negative and the fluid is normal in all other respects." This is, in most cases, equivalent to a life sentence. Again, antediluvian mysticism rears its head. "Most authorities now agree that syphilis is a cause of mental deficiency." "It is not essential for the treponema to be transferred to the patient, because parental syphilis may undoubtedly give rise to retarded cerebral and mental development."

Affections of the eyes and ears are adequately covered. There follows an interesting discussion of third-generation syphilis with several likely cases. Recommendations as to treatment include a combination of penicillin, Mapharsen, and bismuth in repeated courses until the "W. R." becomes negative. These would, in this country at least, be considered archaic.

Richard D. Hahn

LUNG CANCER. By Seymour M. Farber, M.D., Associate Clinical Professor of Medicine, University of California Medical School; Lecturer in Diseases of the Chest, University of California School of Public Health. Pp. 157; indexed. Springfield, 1954, Charles C Thomas, Publisher. Price $4.75.

This monograph represents the crystallization of the author's conclusions based on ten years of special study of lung cancer, including analysis of over 1,000 autopsied cases and of an additional 3,000 suspected cases studied by cytologic and other clinical diagnostic methods. It is primarily a personal book presenting an individual point of view. The contributions and opinions of others, especially of workers in basic research, are presented but the work is not an exhaustive review of the subject. The approach is that of the clinician, and the volume is directed to the clinician, in particular to the general practitioner.

The growing importance of exfoliative cytology in diagnosis is stressed, and this subject is particularly well presented. The author's special interest in chemotherapy of cancer is also apparent in the excellent discussion of the various agents available. Although the effectiveness of these agents in lung cancer is limited at best, they are often too summarily dismissed from practical consideration. Many roentgenologists and experienced clinicians, however, will disagree with the thesis that chemotherapy (with presently available agents) is more promising than radiation, or that x-ray treatment should be reserved for the treatment of symptoms due to bone or nerve involvement.

There is little that is factually new in this monograph, and much is lacking that would make the presentation of the subject more complete. For instance, in the chapter on histopathology there is mention of terminal bronchiolar or "alveolar cell" carcinoma but no mention of the frequent resemblance of this variety of lung cancer to pulmonary adenomatosis; nor is there any clinical description of this syndrome. Similarly, there is no discussion of the potential malignancy of bronchial adenoma, or of the relationship of this to the more typical varieties of malignant bronchial tumors. Despite such omissions, the book is a valuable contribution and will be read with profit by all those who have an interest in this disease. The spectacular increase in prevalence of lung cancer and its probable relation to the widespread habit of smoking make it a subject of interest to virtually all medical practitioners. This timely publication should have a large number of readers.

Carl Muschenheim